PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference 440423C	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00003**	International Filing Date *(day/month/year)* 5 January 2000	Priority Date *(day/month/year)* 5 January 1999
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07D 487/08; C07F 1/08; A61K 51/02; 49/12; 49/14; 49/16		
Applicant AUSTRALIAN NUCLEAR SCIENCE & TECHNOLOGY ORGANISATION et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheet(s).

3. This report contains indications relating to the following items:

I	☒	Basis of the report
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
4 August 2000	19 December 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **K. LEVER** Telephone No. (02) 6283 2254

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00003

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-34,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☒ the claims, pages , as originally filed,
pages **40-44** , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

☒ the drawings, pages **1/8-8/8** , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos: **1-6 in part and 8-23 in part.**

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. **1-6 in part and 8-23 in part (original claim 1-7 in part and 9-24 in part) because of the broad scope of the claims.**

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00003

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	**1-6 in part and 8-23 in part , 7**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**1-6 in part and 8-23 in part , 7**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1-23**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

Citations:

WO 95/31202

WO 90/12050

Nucl. Med. Biol. 1991 Vol 18, No 8 Pages 855-858.

Aust. J. Chem. 1993, 46, pages 1485-1505.

Inorg. Chem.1991, Vol 38. No.22, pages 5086-5090

Explanations:

The cited documents do not disclose nor fairly suggest the compounds of the new claims. The term functional linkage group is now well defined and is not disclosed or suggested in the cited documents. Therefore claims 1-6 in part and claim 7 and claims 8-23 in part are considered novel and inventive. All the claims are considered to be Industrially Applicable.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

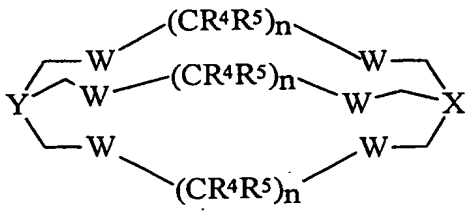
The claims are not fully supported by the description and examples. The claims are broad and encompass many different structures and the only one that appears to be exemplified is that where W is NH and n is 2. This is what the search has been limited too and thus the reason behind only part of the claims being deemed novel and inventive.

There is no support in the description for the other structures.

Please note that there are now two sets of claims in the specification this can be rectified in the National Phase.

CLAIMS

1. A compound which is capable of being radiolabelled of general formula (I) which is as follows:



(I)

in which n represents an integer from 2 to 4,
where each R^4 and R^5 is independently selected from -H, CH_3, COOH, NO_2, CH_2OH, H_2PO_4, HSO_3, CN, $C(=O)NH_2$ and CHO;

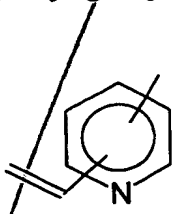
X and Y are the same or different and are selected from the group consisting of C-R, N, P and C-Z in which R is selected from hydrogen, halogen, hydroxyl, nitro, nitroso, amino, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, cyano, COOR', COCOOR', NH-$COCH_2$Br and -NH-CO-CH=CH-COOR' in which R' is a hydrogen atom or alkyl group;

W is selected from the group consisting of NH, S and O; and

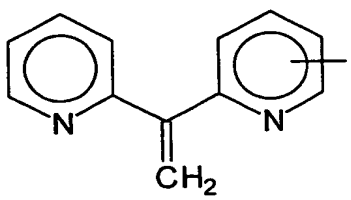
Z is a functionalised linkage group which is capable of binding said compound of formula (I) to a molecular recognition unit and wherein at least one of X and Y is C-Z; or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the molecular recognition unit is selected from the group consisting of an antibody, protein, peptide, carbohydrate, nucleic acid, oligonucleotide, oligosaccharide and liposome.

3. A compound according to claim 1, wherein the functionalised linkage group Z of the compound of Formula (I) is selected from the group consisting of halogen, maleimide, a vinyl pyridyl group of formula

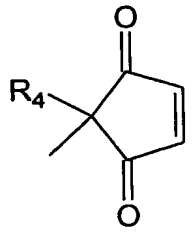


or



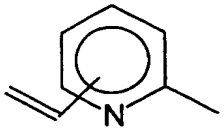
a dione of formula

Replaced by Article 19

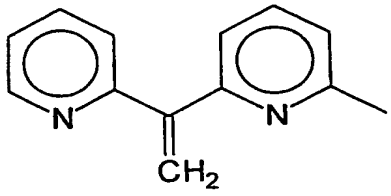


a substituted vinyl group of formula Het^1-C(Het^2)=CH_2 where Het^1 and Het^2 are the same or different and is each a nitrogen containing heterocyclic group or Het^1 is a nitrogen containing heterocyclic group and Het^2 is H, -C(=NH)OR^2, NCO, NCS, COR", COOR', SR^2, $NHNR^2R^3$, $NHCONHNR^2R^3$, $NHCSNHNR^2R^3$, $CONR^2$, OR^2, NR^2R^3, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$, and $(CHCH)_rArR^1$ where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$ and $(CHCH)_rArR^1$ and where R^1 is selected from SH, OH, NH_2, COOH, NCS, -N=N, or -C(=NH)OCH_3 and, COR", where R" is H, halogen, N_3, alkoxy, OAr, imidyloxy, imidazoyloxy, alkyl, or alkyl substituted with a halogen or other leaving group, where p is an integer from 1 to 20, q is an integer from 1 to 20, r is an integer from 1 to 4, and Ar is optionally substituted aryl or optionally substituted aralkyl, provided that when one of X and Y is selected from C-NO_2, C-OH, C-Cl, C-CH_3 or C-NH_2 then the other X or Y substituent cannot be selected from C-NO_2, C-OH, C-Cl or C-NH_2.

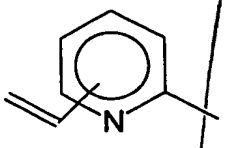
4. A compound according to claim 3, wherein the functionalised linkage group Z of the compound of Formula (I) is a vinyl pyridyl group of formula

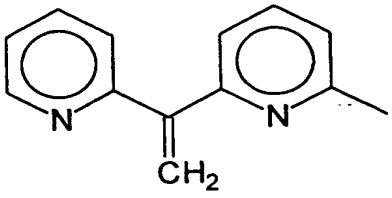


or

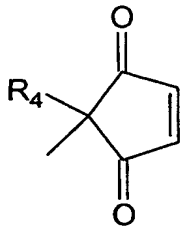


5. A compound according to claim 1, wherein the functionalised linkage group Z of the compound of Formula (I) is selected from





a dione of formula



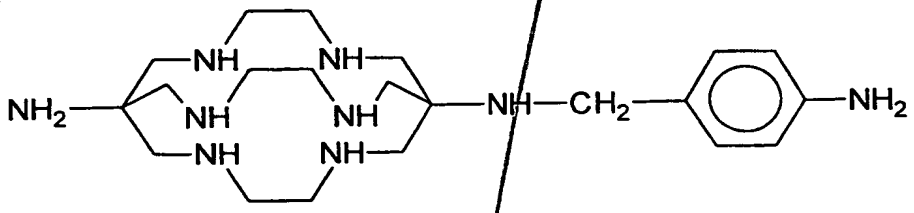
, and

NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $-(CH_2OCH_2O)_qArR^1$, $-(CHCH)_rR^1$, and $(CHCH)_rArR^1$ and where R^1 is selected from NH_2, COOH, NCS, NCO, -N=N, $-C(=NH)OCH_3$, and COR" where R" is H, halogen, alkyl, or alkyl substituted with a halogen or other leaving group, where p is an integer from 1 to 20; q is an integer from 1 to 20; r is an integer from 1 to 4; and Ar is optionally substituted aryl or optionally substituted aralkyl, provided that at least one of R^2 and R^3 is other than hydrogen.

6. A compound according to claim 1, wherein W is NH and Z is selected from NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, and $(CH_2)_pArR^1$; R^1 is selected from NH_2, COOH and NCS; and p is an integer from 1 to 4.

7. A compound according to claim 5, wherein the Z group of said compound of Formula (I) is NR^2R^3 where R^2 and R^3 together with the nitrogen atom to which they are attached form an optionally substituted saturated or partially unsaturated ring optionally containing one or more further heteroatoms O, S or N whereby there is at least one substituent capable of binding said compound of Formula (I) with a molecular recognition unit.

8. A compound of Formula (I) having the following structure:



9. A compound according to claim 1, wherein said compound is complexed with a metal ion.

10. A compound according to claim 9 wherein the metal ion is selected from Cu, Tc, Gd, Ga, In, Y, Co, Re, Fe, Au, Ag, Rh, Pt, Bi, Cr, W, Ni, V, Pb, Ir, Pt, Zn, Cd, Mn, Ru, Pd, Hg, Ti, and the lanthanide group of elements in the Periodic Table such as Sm, Ho, Gd, Tb, Sc.

11. A compound according to claim 10 wherein the metal ion is a radionuclide selected from the group of Cu, Cu, Tc, In, Gd, Ga, Fe, Cu, Ti and other radionuclides from the Lanthanides, Re, Sm, Ho, and Y .

12. A compound according to claim 11 wherein the radionuclide is selected from the group of ^{64}Cu, ^{67}Cu and ^{99m}Tc.

13. A pharmaceutical formulation comprising a compound according to claim 1, a radiolabelled complex or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

14. A diagnostic formulation comprising a compound according to claim 1, a radiolabelled complex or pharmaceutically acceptable salt thereof and a reducing agent in a pharmaceutically acceptable carrier.

15. A method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof.

16. Use of a compound according to claim 1 or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof in the preparation of a medicament for diagnosis or therapy of disease in a subject.

17. A compound according to claim 1 or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof when used in the diagnosis or therapy of disease in a subject.

18. A conjugate compound comprising at least one compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof bonded to at least one molecular recognition unit comprising an antibody, protein, peptide, carbohydrate, oligonucleotide, oligosaccharide.

19. A method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a conjugate compound according to claim 18.

20. Use of a conjugate compound according to claim 18 in the preparation of a medicament for diagnosis or therapy of disease in a subject.

21. A conjugate compound as described in claim 1 when used in the diagnosis or therapy of disease in a subject.

22. A method of imaging a subject comprising introducing a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof to a subject.

23. Use of a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof in the preparation of a medicament for imaging in a subject.

24. A compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof when used in imaging in a subject.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SPRUSON & FERGUSON
GPO Box 3898
SYDNEY NSW 2001

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *day/month/year* 02 .....

Applicant's or agent's file reference
440423C

IMPORTANT NOTIFICATION

International Application No.	International Filing Date	Priority Date
PCT/AU00/00003	5 January 2000	5 January 1999

Applicant
AUSTRALIAN NUCLEAR SCIENCE & TECHNOLOGY ORGANISATION et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide

Name and mailing address of the IPEA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	K. LEVER Telephone No. (02) 6283 2254

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 440423C	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00003**	International Filing Date *(day/month/year)* 5 January 2000	Priority Date *(day/month/year)* 5 January 1999
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07D 487/08; C07F 1/08; A61K 51/02; 49/12; 49/14; 49/16		
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VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

Date of submission of the demand 4 August 2000	Date of completion of the report 19 December 2000
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **K. LEVER** Telephone No. (02) 6283 2254

[redacted] International application No.
PCT/AU00/00003

[redacted] the international application:*
[redacted] application as originally filed.

[redacted] description, pages 1-34, as originally filed,
pages , filed with the demand,
pages , received on with the letter of *

[X] the claims, pages , as originally filed,
pages 40-44 , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages , received on with the letter of

[X] the drawings, pages 1/8-8/8 , as originally filed,
pages , filed with the demand,
pages , received on with the letter of

[ ] the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

BEST AVAILABLE COPY

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

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[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

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[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/fig.

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00003

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be nonobvious), or to be industrially applicable have not been examined in respect of:

☐ * the entire international application,

☒ claims Nos: **1-6 in part and 8-23 in part.**

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. **1-6 in part and 8-23 in part (original claim 1-7 in part and 9-24 in part) because of the broad scope of the claims.**

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00003

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6 in part and 8-23 in part , 7	YES
	Claims		NO
Inventive step (IS)	Claims	1-6 in part and 8-23 in part , 7	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-23	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Citations:

WO 95/31202

WO 90/12050

Nucl. Med. Biol. 1991 Vol 18, No 8 Pages 855-858.

Aust. J. Chem. 1993, 46, pages 1485-1505.

Inorg. Chem.1991, Vol 38. No.22, pages 5086-5090

Explanations:

The cited documents do not disclose nor fairly suggest the compounds of the new claims. The term functional linkage group is now well defined and is not disclosed or suggested in the cited documents. Therefore claims 1-6 in part and claim 7 and claims 8-23 in part are considered novel and inventive. All the claims are considered to be Industrially Applicable.

ONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00003

Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The claims are not fully supported by the description and examples. The claims are broad and encompass many different structures and the only one that appears to be exemplified is that where W is NH and n is 2. This is what the search has been limited too and thus the reason behind only part of the claims being deemed novel and inventive.

There is no support in the description for the other structures.

Please note that there are now two sets of claims in the specification this can be rectified in the National Phase.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 440423C

Box No. I TITLE OF INVENTION

Cryptate Compounds and Methods for Diagnosis and Therapy

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

AUSTRALIAN NUCLEAR SCIENCE & TECHNOLOGY ORGANISATION
New Illawarra Road,
Lucas Heights, New South Wales 2234
AUSTRALIA

☐ This person is also inventor.

Telephone No. 9717 3111

Facsimile No. 9717 9272

Teleprinter No.

State *(i.e. country)* of nationality: AUSTRALIA

State *(i.e. country)* of residence: AUSTRALIA

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United states of America ☐ the United states of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

THE AUSTRALIAN NATIONAL UNIVERSITY
Chancelry East Road
Acton, Australian Capital Territory 2601
AUSTRALIA

This person is:

☒ applicant only
☐ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AUSTRALIA

State *(i.e. country)* of residence: AUSTRALIA

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United states of America ☐ the United states of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)*

SPRUSON & FERGUSON
GPO BOX 3898
Sydney
New South Wales 2001
AUSTRALIA

Telephone No. (02) 9207 0777

Facsimile No. (02) 9232 8555

Teleprinter No AA 23165

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Sheet No. 2

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

SMITH, Suzanne Virginia
9 Kitchener Road
Caringbah, New South Wales 2229
AUSTRALIA

This person is :
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AUSTRALIA

State *(i.e. country)* of residence: AUSTRALIA

This person is applicant for the purposes of : ☐ all designated States ☐ all designated States except the United states of America ☒ the United states of America only ☐ The States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)*

HARROWFIELD, John M.
19 Willcock Avenue
Daglish, Western Australia, 6008
AUSTRALIA

This person is :
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AUSTRALIA

State *(i.e. country)* of residence: AUSTRALIA

This person is applicant for the purposes of : ☐ all designated States ☐ all designated States except the United states of America ☒ the United states of America only ☐ The States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)*

DI BARTOLO, Nadine Maric
54 Glencoe Street
Sutherland, New South Wales 2232
AUSTRALIA

This person is :
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AUSTRALIA

State *(i.e. country)* of residence: AUSTRALIA

This person is applicant for the purposes of : ☐ all designated States ☐ all designated States except the United states of America ☒ the United states of America only ☐ The States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country)*

SARGESON, Alan McLeod
53 Dunstan Street
Curtin, Australian Capital Territory, 2605
AUSTRALIA

This person is :
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: AUSTRALIA

State *(i.e. country)* of residence: AUSTRALIA

This person is applicant for the purposes of : ☐ all designated States ☐ all designated States except the United states of America ☒ the United states of America only ☐ The States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Tukmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden , and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

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☒	KE	Kenya	☒	ZA	South Africa
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See Notes to the request form

Sheet No. 4

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) AUSTRALIA	(05/01/2000) 5 January 1999	PP8038	
item (2)			
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

☒ The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s) : (1)

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA/_____

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office): Date *(day/month/year)* Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	:	4 sheets
2. description	:	34 sheets
3. claims	:	5 sheets
4. abstract	:	1 sheets
5. drawings	:	8 sheets
Total	:	52 sheets

This international application is accompanied by the item(s) marked below:

1. ☐ separate signed power of attorney
2. ☐ copy of general power of attorney
3. ☐ statement explaining lack of signature
4. ☐ priority document(s) *identified in Box No. VI as item(s):*
5. ☒ fee calculation sheet
6. ☐ separate indications concerning deposited microorganisms
7. ☐ nucleotide and/or amino acid sequence listing (diskette)
8. ☐ other *(specify):*

Figure No. of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

Andrew Bluttman
Registered Patent Attorney
SPRUSON & FERGUSON

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1. Date of actual receipt of the purported international application:
2. Drawings ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
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5. International Searching Authority specified by the applicant: ISA/
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 487/08, C07F 1/08, A61K 51/02, 49/12, 49/14, 49/16 — A1

(11) International Publication Number: **WO 00/40585**

(43) International Publication Date: 13 July 2000 (13.07.00)

(21) International Application Number: PCT/AU00/00003

(22) International Filing Date: 5 January 2000 (05.01.00)

(30) Priority Data:
PP 8038 5 January 1999 (05.01.99) AU

(71) Applicants *(for all designated States except US)*: AUSTRALIAN NUCLEAR SCIENCE & TECHNOLOGY ORGANISATION [AU/AU]; New Illawarra Road, Lucas Heights, NSW 2234 (AU). THE AUSTRALIAN NATIONAL UNIVERSITY [AU/AU]; Chancelry East Road, Acton, ACT 2601 (AU).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SMITH, Suzanne, Virginia [AU/AU]; 9 Kitchener Road, Caringbah, NSW 2229 (AU). HARROWFIELD, John, M. [AU/AU]; 19 Willcock Avenue, Daglish, W.A. 6008 (AU). DI BARTOLO, Nadine, Marie [AU/AU]; 54 Glencoe Street, Sutherland, NSW 2232 (AU). SARGESON, Alan, McLeod [AU/AU]; 53 Dunstan Street, Curtin, ACT 2605 (AU).

(74) Agent: SPRUSON & FERGUSON; GPO Box 3898, Sydney, NSW 2001 (AU).

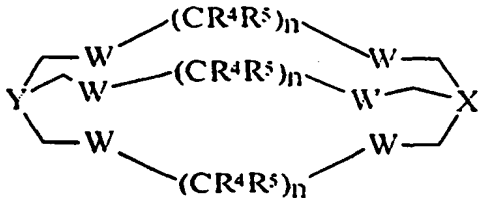
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: CRYPTATE COMPOUNDS AND METHODS FOR DIAGNOSIS AND THERAPY

(57) Abstract

The present invention relates to cryptate compounds useful as chelating agents. In particular, the present invention relates to functionalised derivatives of certain cryptate compounds. These functionalised derivatives are suitable for use in radiolabelling and similar applications. The present invention also relates to a method for diagnosis or therapy of a disease utilising functionalised derivatives of cryptase compounds. In one embodiment, the present invention relates to a compound which is capable of being radiolabelled of general formula (I) in which n represents an integer from 2 to 4, where each R^4 and R^5 is independently selected from –H, CH_3, COOH, NO_2, CH_2OH, H_2PO_4, HSO_3, CN, $C{=}ONH_2$ and CHO; X and Y are the same or different and are selected from the group of C–R, N, P and C–Z in which R represents a hydrogen or halogen atom or a hydroxyl, nitro, nitroso, amino, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or cyano group, or a group of the formula –COOR', COCOOR', NH–$COCH_2Br$, –NH–CO–CH=CH–COOR' in which R' is a hydrogen atom or alkyl group; or; W is selected from the group of NH, S and O; and Z is a functionalised linkage group which is capable of binding said compound of formula (I) to a molecular recognition unit and wherein at least one of X and Y is C–Z; or a pharmaceutically acceptable salt thereof.



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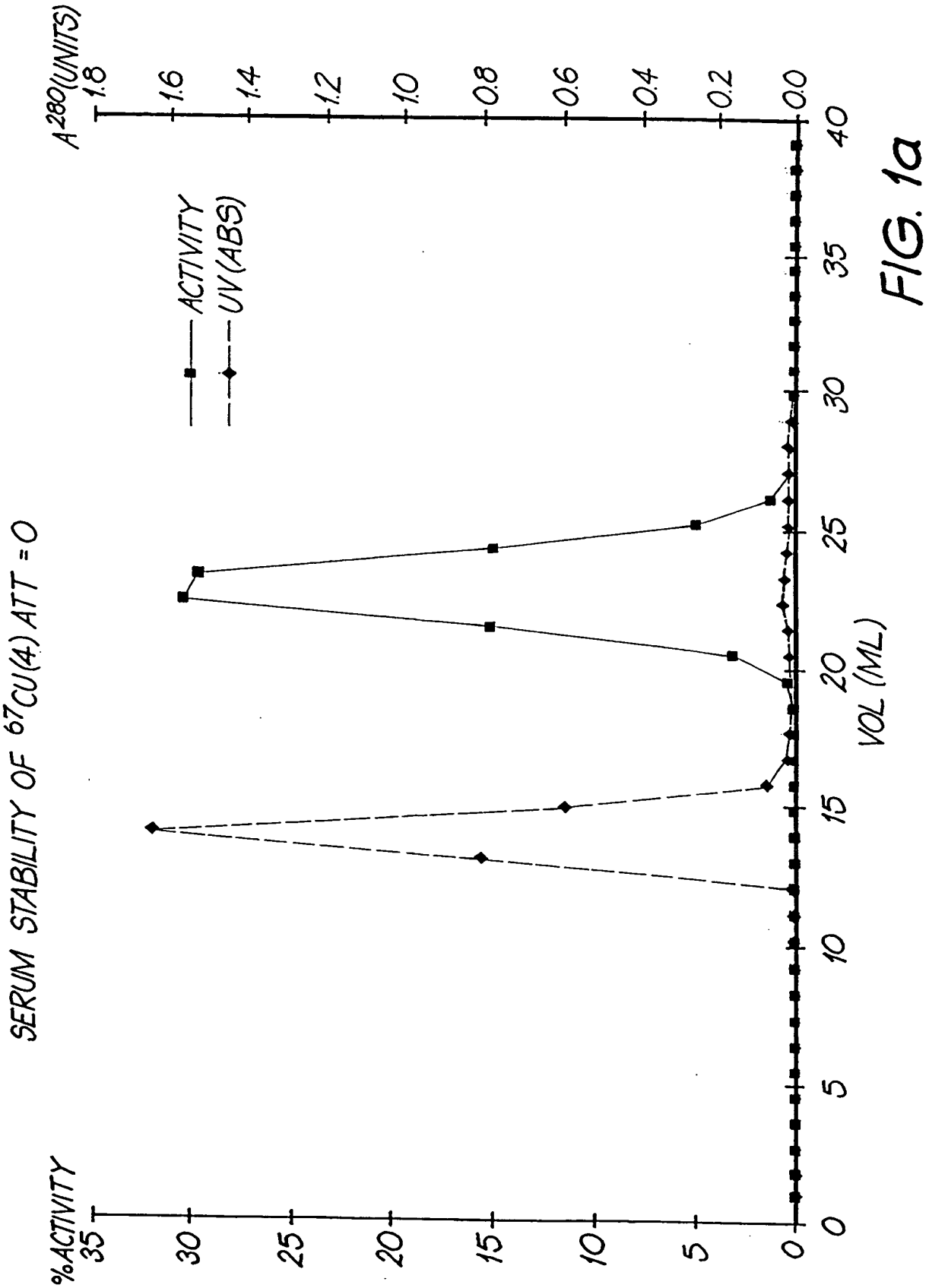
EE	Estonia	**LR**	Liberia	**SG**	Singapore		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ACTIVITY
UV(ABS)
VOL (ML)
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15
20
25
30
35
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0.6
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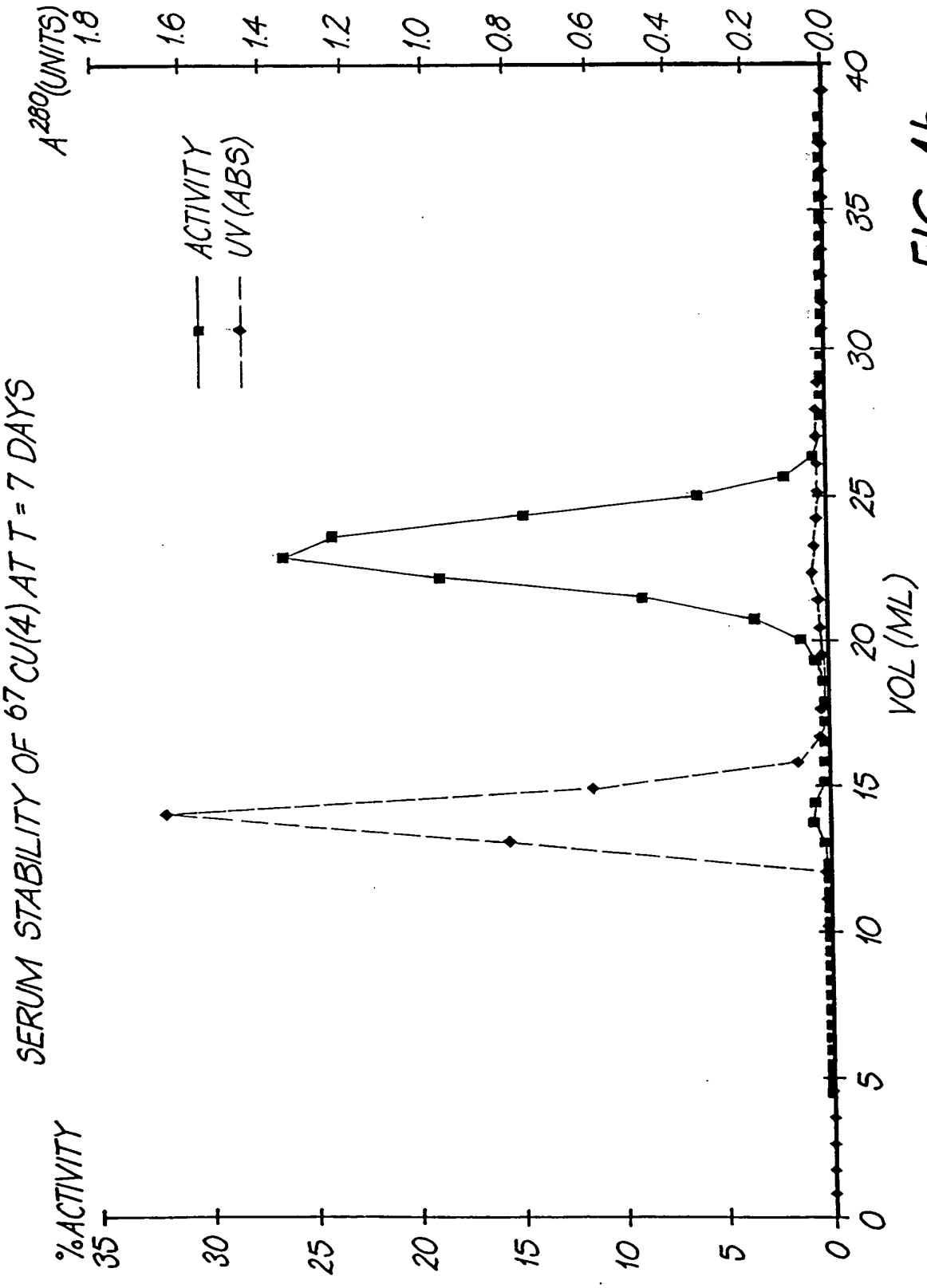
FIG. 1a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A 280 (UNITS)
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UV (ABS)
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5
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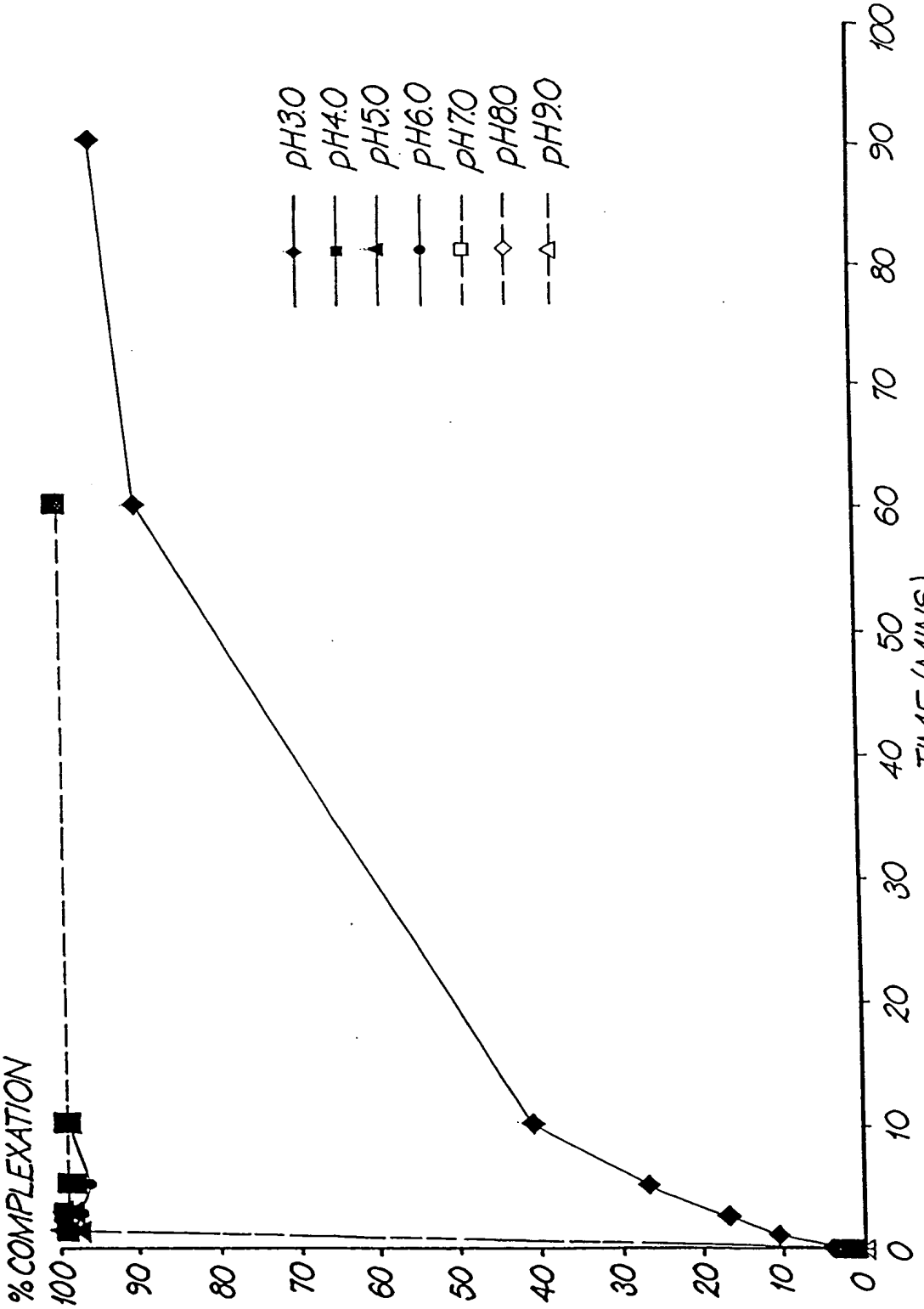
FIG. 1b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30
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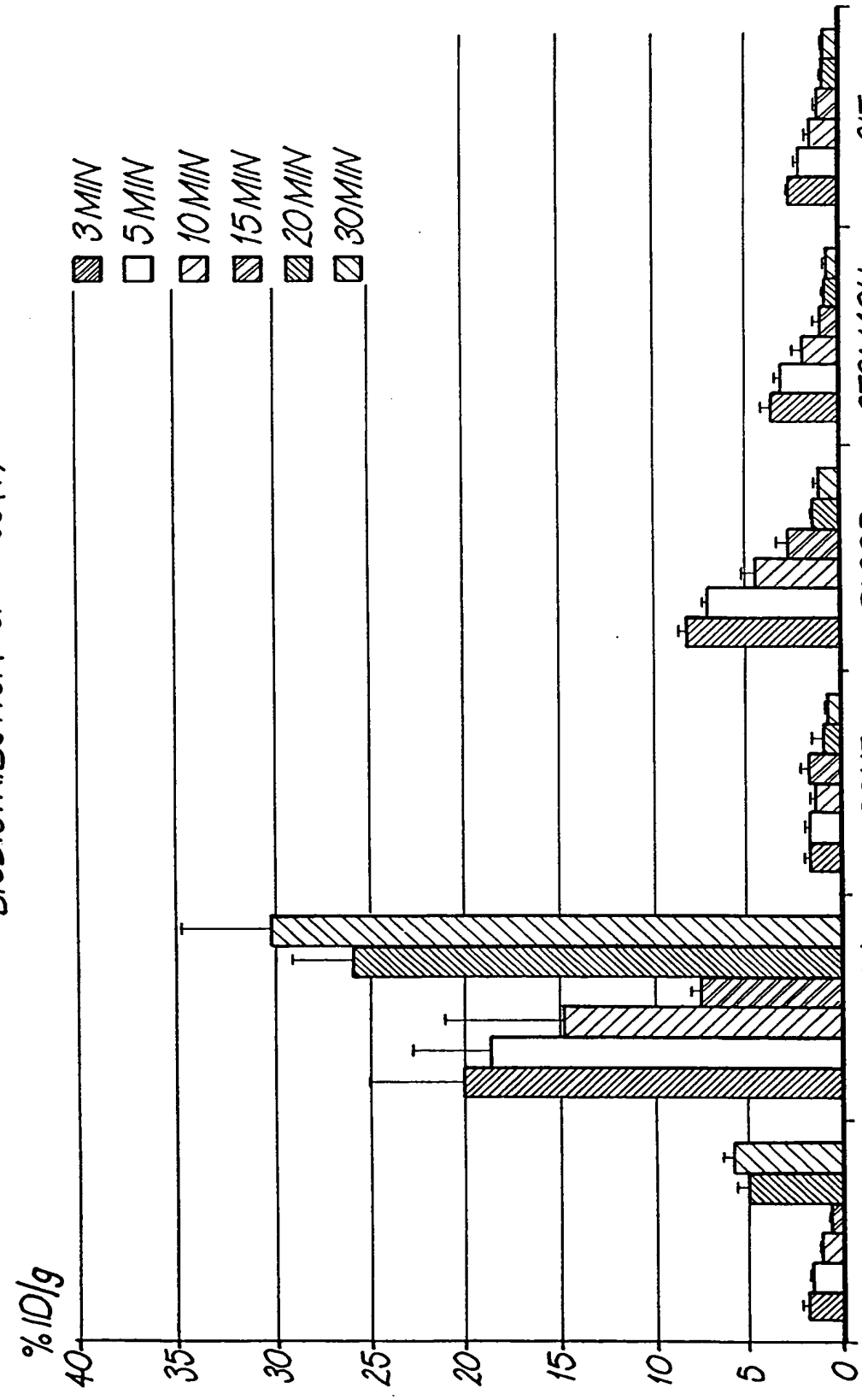
FIG. 2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% ID/g
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35
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25
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15
10
5
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5 MIN
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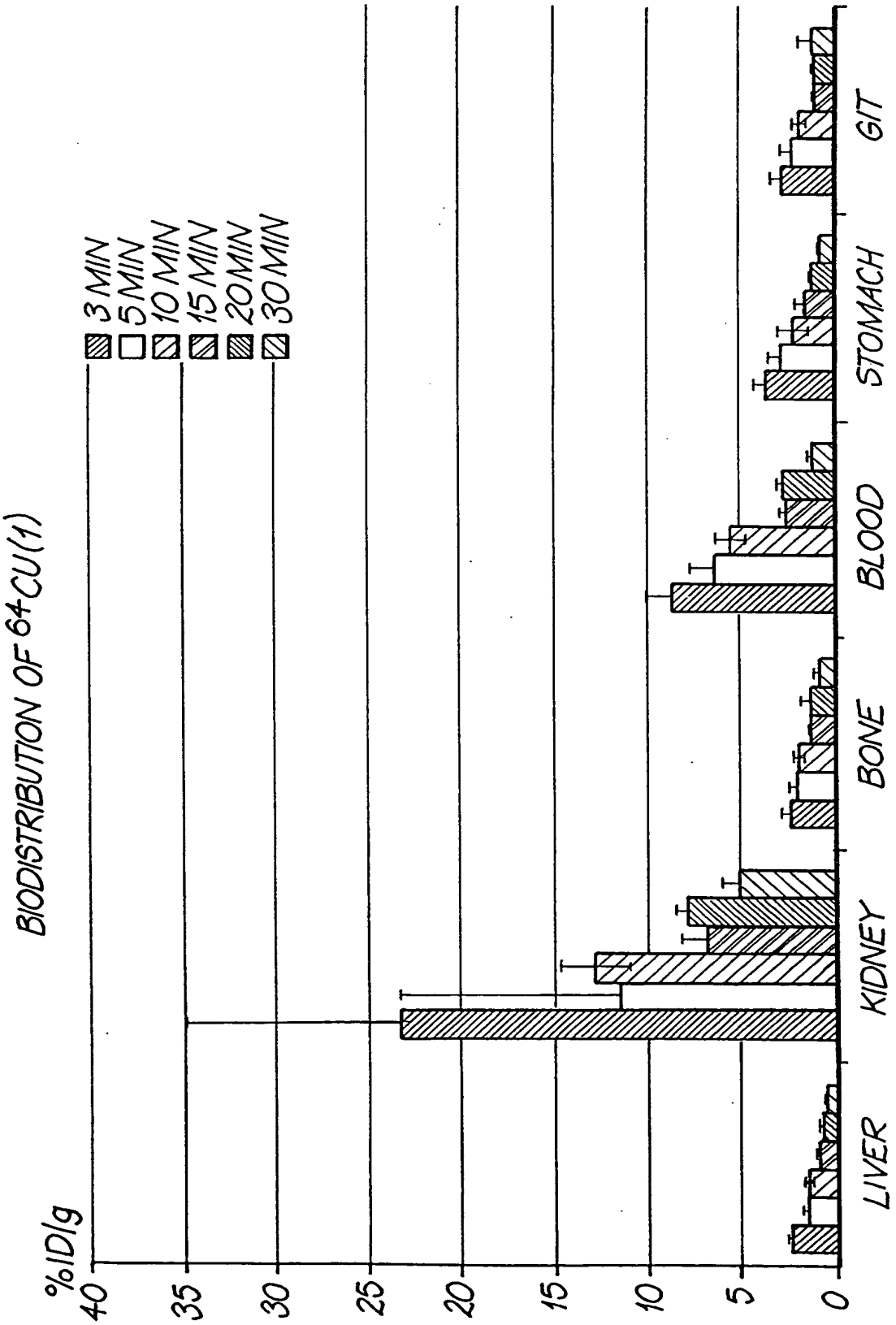
30 MIN
LIVER
KIDNEY
BONE
BLOOD
STOMACH
GIT
ORGAN

FIG. 3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%ID/g
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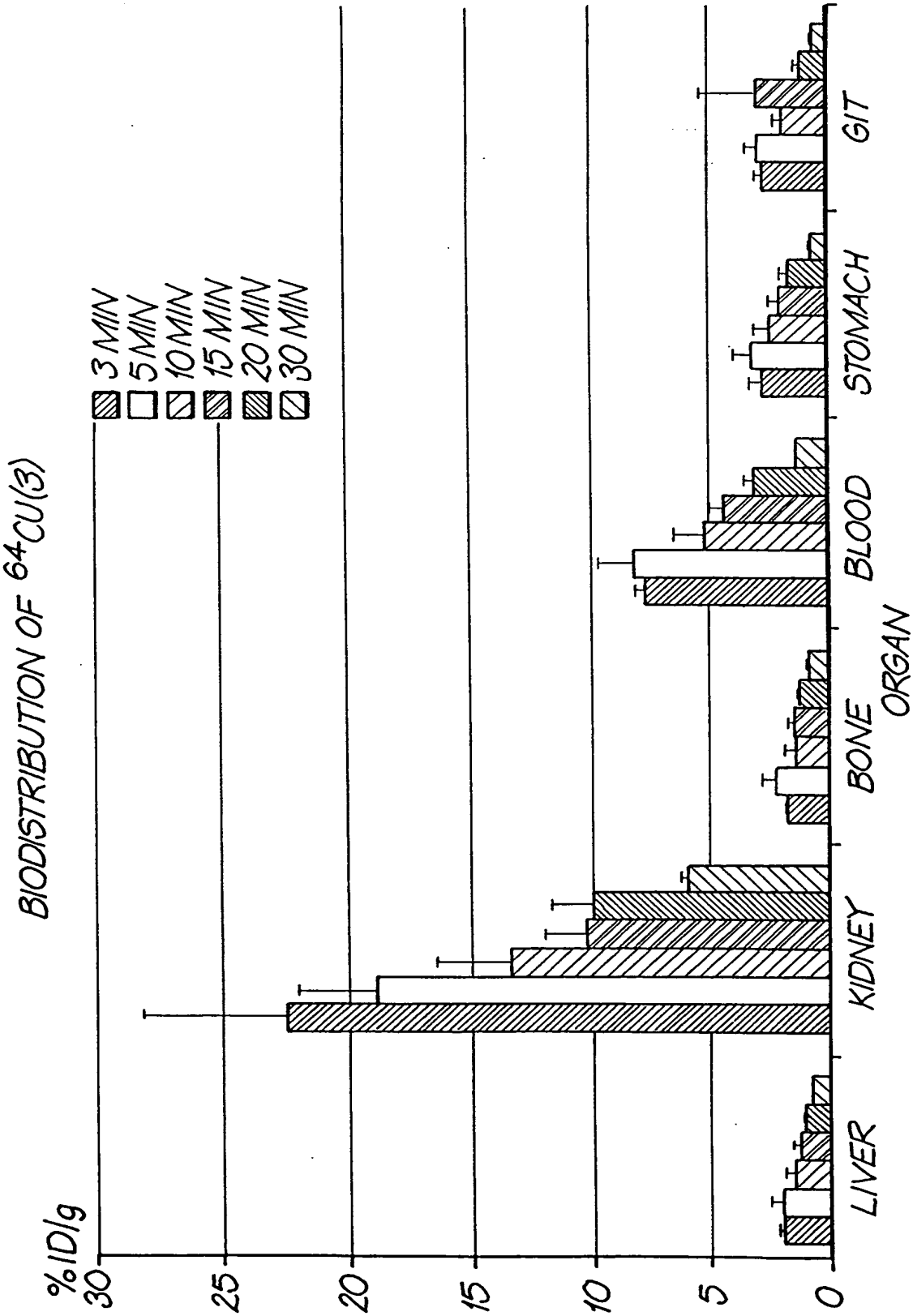
KIDNEY
BONE
BLOOD
STOMACH
GIT
ORGAN

FIG. 4


BIODISTRIBUTION OF ^{64}CU(3)
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30
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LIVER
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ORGAN

FIG. 5

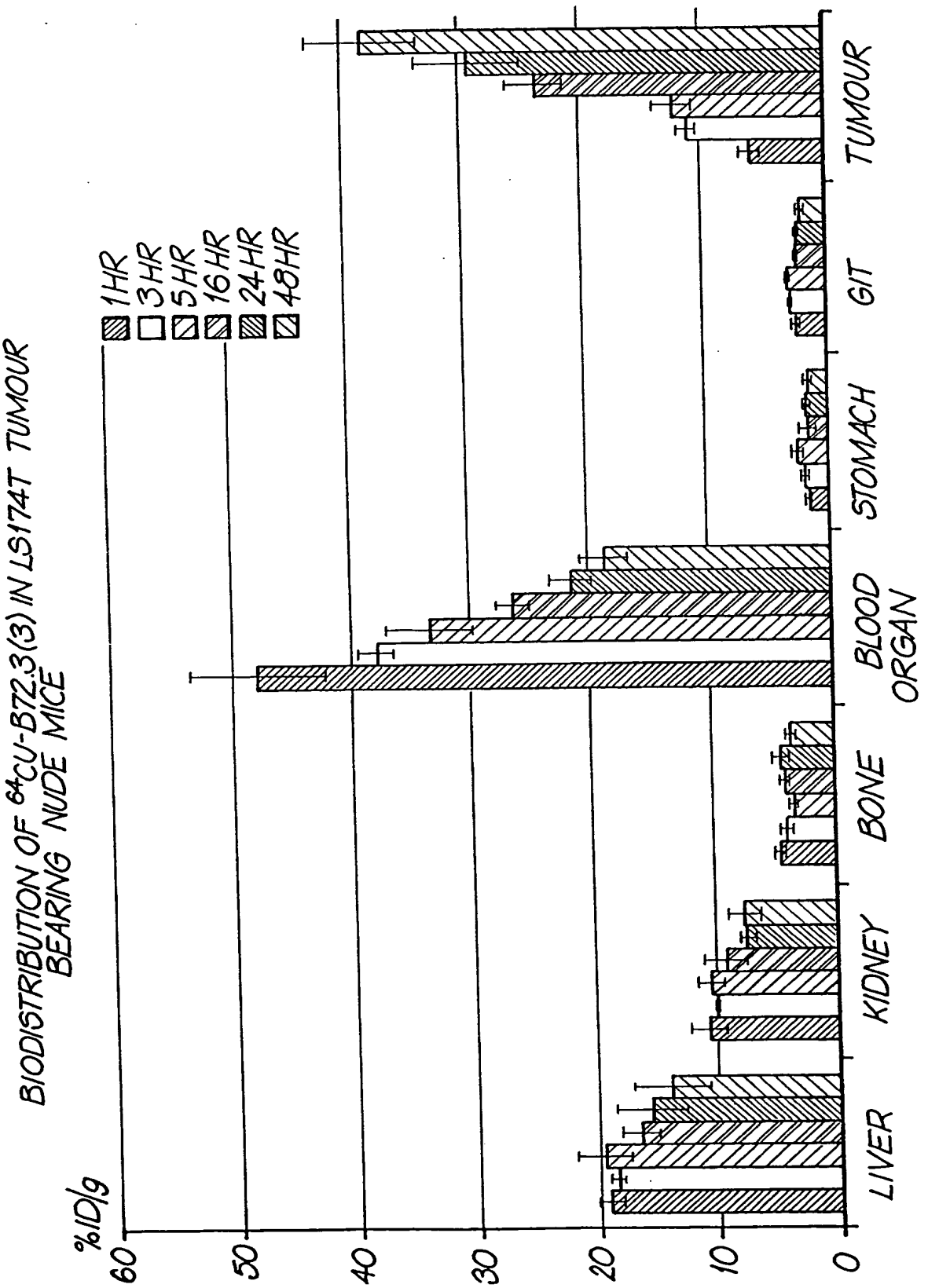
BIODISTRIBUTION OF ^{64}CU-B72.3(3) IN LS174T TUMOUR BEARING NUDE MICE
1HR
3HR
5HR
16HR
24HR
48HR
%ID/g
60
50
40
30
20
10
0
LIVER
KIDNEY
BONE
BLOOD
ORGAN
STOMACH
GIT
TUMOUR

FIG. 6

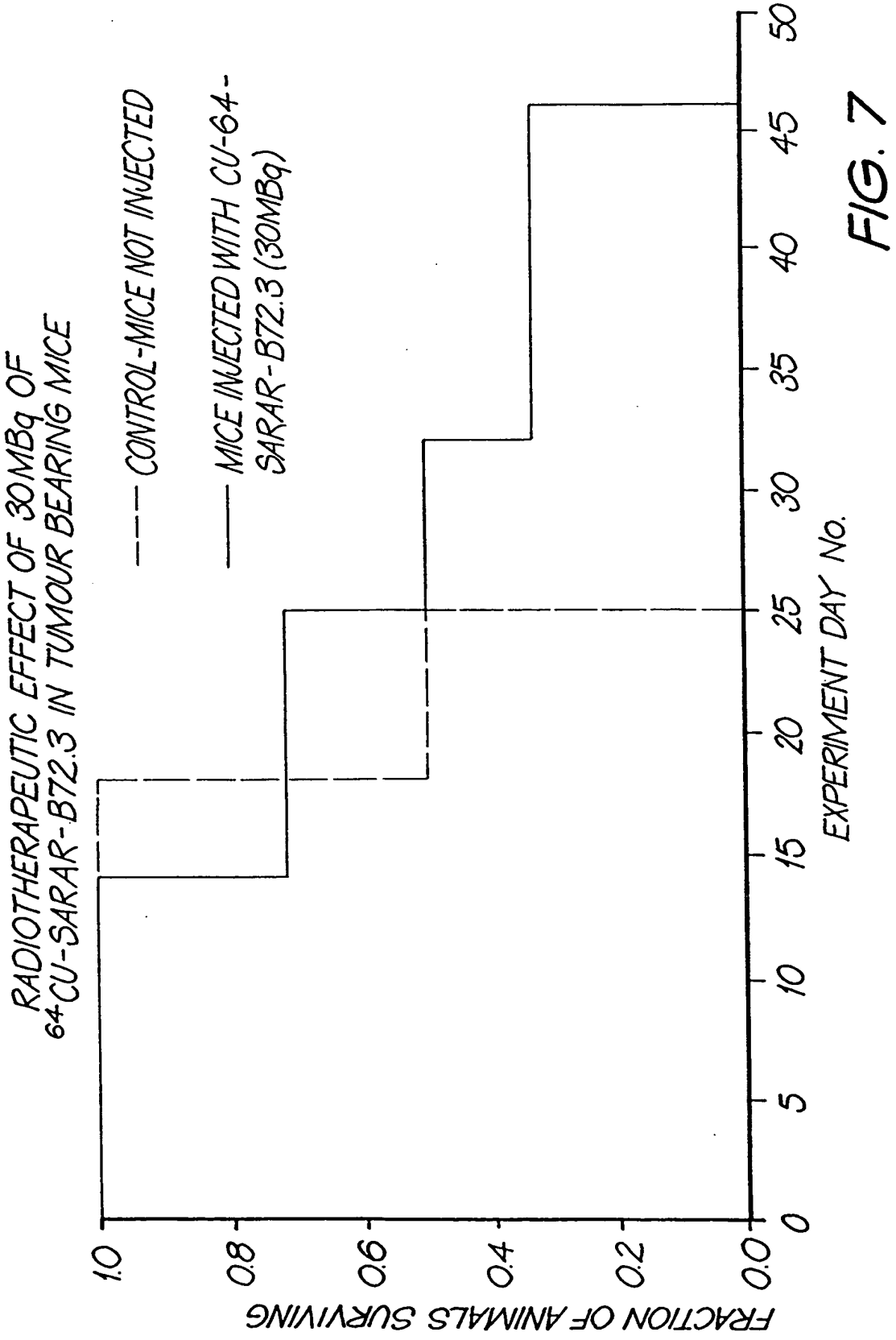
RADIOTHERAPEUTIC EFFECT OF 30MBq OF
64CU-SARAR-B72.3 IN TUMOUR BEARING MICE
--- CONTROL-MICE NOT INJECTED
— MICE INJECTED WITH CU-64-SARAR-B72.3 (30MBq)
FRACTION OF ANIMALS SURVIVING
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
35
40
45
50
EXPERIMENT DAY No.

FIG. 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00003

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 487/08; C07F 1/08; A61K 51/02, 49/12, 49/14, 49/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN SUBSTRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/31202 A (COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANISATION) publication date 13 November 1995. See in particular page 4, last paragraph and table 1..	1-7,9,10
X	WO 90/12050 A (SALUTAR INC) publication date 18 October 1990. See in particular pages 3-4.	1,2,6,9-13,15-17,22-24
X	Nucl. Med. Biol. Vol 18. No. 8. Pages 855-858, 1991 Int. J. Radiat. Appl. Instrum. Part B 'Chromium-Caged Complex as Contrast Agent in MR Imaging- Biodistribution Studies of the [^{57} Co] Cobalt Analogue'	1,2,6,9,10,13,15,16,17, 22-24

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 February 2000	- 8 MAR 2000
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	K. LEVER Telephone No.: (02) 6283 2254

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00003

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Aust. J. Chem., 1993, 46, pages 1485-1505. Clark et al, 'Structural Characterization of Encapsulation Reactions Based on the Tris(ethane-1,2-diamine) cobalt (II) Ion.'	1,2,9,10
X	Inorg. Chem. 1995, Vol 34. No. 14, pages 3589-3599 Bernhardt et al, 'Copper (II) Complexes of substituted Macrobicyclic Hexaamines:' see page 3597.	1
X	Inorg. Chem. 1999, Vol 38. No. 22, pages 5086-5090 Bernhardt et al, 'Electrochemistry of Marcrocyclic Cobalt (III/II) Hexaamines: Electrocatalytic Hydrogen Evolution in Aqueous Solution'.	9,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00003

Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:1-7 in part 9-24 in part
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The search has been restricted for economical reasons to the compound of claim 8 and the structure of the compound of claim 1 where W is NH and n is 2.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU00/00003

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	95/31202	AU	24397/95	ZA	9504017		
WO	90/12050	AU	54235/90	CA	2051648	DE	69027603
		EP	474642				

END OF ANNEX

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 487/08, C07F 1/08, A61K 51/02, 49/12, 49/14, 49/16 — **A1**

(11) International Publication Number: **WO 00/40585**

(43) International Publication Date: 13 July 2000 (13.07.00)

(21) International Application Number: PCT/AU00/00003

(22) International Filing Date: 5 January 2000 (05.01.00)

(30) Priority Data:
PP 8038 5 January 1999 (05.01.99) AU

(71) Applicants *(for all designated States except US)*: AUSTRALIAN NUCLEAR SCIENCE & TECHNOLOGY ORGANISATION [AU/AU]; New Illawarra Road, Lucas Heights, NSW 2234 (AU). THE AUSTRALIAN NATIONAL UNIVERSITY [AU/AU]; Chancelry East Road, Acton, ACT 2601 (AU).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SMITH, Suzanne, Virginia [AU/AU]; 9 Kitchener Road, Caringbah, NSW 2229 (AU). HARROWFIELD, John, M. [AU/AU]; 19 Willcock Avenue, Daglish, W.A. 6008 (AU). DI BARTOLO, Nadine, Marie [AU/AU]; 54 Glencoe Street, Sutherland, NSW 2232 (AU). SARGESON, Alan, McLeod [AU/AU]; 53 Dunstan Street, Curtin, ACT 2605 (AU).

(74) Agent: SPRUSON & FERGUSON; GPO Box 3898, Sydney, NSW 2001 (AU).

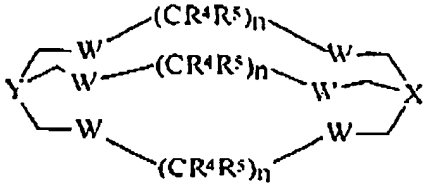
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

(54) Title: CRYPTATE COMPOUNDS AND METHODS FOR DIAGNOSIS AND THERAPY

(57) Abstract

The present invention relates to cryptate compounds useful as chelating agents. In particular, the present invention relates to functionalised derivatives of certain cryptate compounds. These functionalised derivatives are suitable for use in radiolabelling and similar applications. The present invention also relates to a method for diagnosis or therapy of a disease utilising functionalised derivatives of cryptase compounds. In one embodiment, the present invention relates to a compound which is capable of being radiolabelled of general formula (I) in which n represents an integer from 2 to 4, where each R^4 and R^5 is independently selected from –H, CH_3, COOH, NO_2, CH_2OH, H_2PO_4, HSO_3, CN, $C{=}ONH_2$ and CHO; X and Y are the same or different and are selected from the group of C–R, N, P and C–Z in which R represents a hydrogen or halogen atom or a hydroxyl, nitro, nitroso, amino, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl or cyano group, or a group of the formula –COOR', COCOOR', NH–$COCH_2$Br, –NH–CO–CH=CH–COOR' in which R' is a hydrogen atom or alkyl group; or; W is selected from the group of NH, S and O; and Z is a functionalised linkage group which is capable of binding said compound of formula (I) to a molecular recognition unit and wherein at least one of X and Y is C–Z; or a pharmaceutically acceptable salt thereof.



(I)

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00003

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 487/08; C07F 1/08; A61K 51/02, 49/12, 49/14, 49/16

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN SUBSTRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 90/12050 A (SALUTAR INC) publication date 18 October 1990. See in particular pages 3-4.	1,2,6,9-13,15-17,22-24
X	Nucl. Med. Biol. Vol 18. No. 8. Pages 855-858, 1991 Int. J. Radiat. Appl. Instrum. Part B 'Chromium-Caged Complex as Contrast Agent in MR Imaging- Biodistribution Studies of the [^{57} Co] Cobalt Analogue'	1,2,6,9,10,13,15,16,17, 22-24

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 February 2000	- 8 MAR 2000
Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	K. LEVER Telephone No.: (02) 6283 2254

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00003

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Aust. J. Chem., 1993, 46, pages 1485-1505. Clark et al, 'Structural Characterization of Encapsulation Reactions Based on the Tris(ethane-1,2-diamine) cobalt (II) Ion.'	1,2,9,10
X	Inorg. Chem.1995, Vol 34. No. 14, pages 3589-3599 Bernhardt et al, 'Copper (II) Complexes of substituted Macrobicyclic Hexaamines:' see page 3597.	1
X	Inorg. Chem.1999, Vol 38. No. 22. pages 5086-5090 Bernhardt et al, 'Electrochemistry of Marcrocyclic Cobalt (III/II) Hexaamines: Electrocatalytic Hydrogen Evolution in Aqueous Solution'.	9,10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU00/00003

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-7 in part 9-24 in part
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The search has been restricted for economical reasons to the compound of claim 8 and the structure of the compound of claim 1 where W is NH and n is 2.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU00/00003

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Patent Document Cited in Search Report		Patent Family Member					
WO	95/31202	AU	24397/95	ZA	9504017		
WO	90/12050	AU	54235/90	CA	2051648	DE	69027603
		EP	474642				

END OF ANNEX

Cryptate Compounds and Methods for Diagnosis and Therapy

Technical Field

The present invention relates to cryptate compounds useful as chelating agents. In particular, the present invention relates to functionalised derivatives of certain cryptate compounds. These functionalised derivatives are suitable for use in radiolabelling and similar applications. The present invention also relates to a method for diagnosis or therapy of a disease utilising functionalised derivatives of cryptate compounds.

Background of the Invention

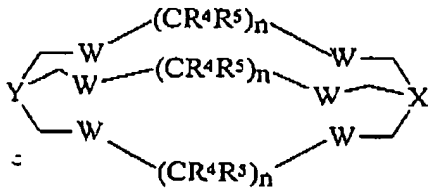
Radiolabelled compounds are useful as radiopharmaceuticals, imaging agents, or the like which are especially useful for but not limited to the diagnosis and therapy of diseases including cancer.

Known radiolabelled compounds suffer from the disadvantage that, in use, the radiolabelled nuclide can become detached from the carrier compound thereby leading to problems and potential complications in diagnostic and therapeutic applications. Further, the known radiopharmaceuticals tend to be non-specific in their biodistribution throughout a subject.

The present invention seeks to ameliorate the stated disadvantages of the prior art by providing compounds which are capable of being radiolabelled more expeditiously, specifically target a localised area of tissue or an organ in a subject and which are more stable than the prior art compounds and less toxic. Further, the compounds of the present invention are typically suitable for use in pharmaceutical formulations. It is a further typical object of the present invention to provide a method of diagnosis or therapy of disease in a subject.

Summary of the Invention

In accordance with a first embodiment of the present invention, there is provided a compound which is capable of being radiolabelled of general formula (I) which is as follows:



(I)

in which n represents an integer from 2 to 4,

where each R^4 and R^5 is independently selected from -H, CH_3, COOH, NO_2, CH_2OH, H_2PO_4, HSO_3, CN, $C(=O)NH_2$ and CHO;

X and Y are the same or different and are selected from the group of C-R, N, P and C-Z in which R is selected from hydrogen, halogen, hydroxyl, nitro, nitroso, amino, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl,

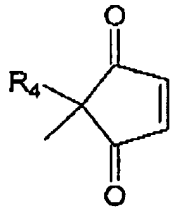
cyano, -COOR', COCOOR', NH-COCH$_2$Br, -NH-CO-CH=CH-COOR' in which R' is a hydrogen atom or alkyl group;

W is selected from the group of NH, S and O; and

Z is a functionalised linkage group which is capable of binding said compound of formula (I) to a molecular recognition unit and wherein at least one of X and Y is C-Z; or a pharmaceutically acceptable salt thereof.

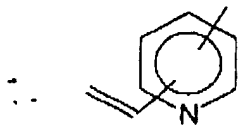
It is to be understood that throughout this specification, the term "molecular recognition unit" includes an antibody, protein, peptide, carbohydrate, nucleic acid, oligonucleotide, oligosaccharide, liposome, or other molecule which can form part of a specific binding pair.

In one form of the compound of Formula (I), the functionalised linkage group Z is selected from the group of halogen or other leaving group, nitro, nitroso, imide, dione of the formula,



vinyl group of formula Het^1-C(Het^2)=CH$_2$ (where Het^1 and Het^2 are the same or different and is each a nitrogen containing heterocyclic group or Het^1 is a nitrogen containing heterocyclic group and Het^2 is H), -C(=NH)OR^2, NCO, NCS, COR", COOR', SR^2, NHNR^{2}R^3, NHCONHNR^{2}R^3, NHCSNHNR^{2}R^3, CONR^2, OR^2, NR^{2}R^3, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$, $(CHCH)_rArR^1$ where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $-(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$, $(CHCH)_rArR^1$ and where R^1 is selected from SH, OH, NH$_2$, COOH, NCS, -N=N, or -C(=NH)OCH$_3$, COR", where R" is H, halogen, N$_3$, alkoxy, OAr, imidyloxy, imidazoyloxy, alkyl, or alkyl substituted with a halogen or other leaving group, where p is an integer from 1 to 20, more typically 1 to 10, still more typically 1 to 4, even more typically 1 to 2 and yet more typically 1; q is an integer from 1 to 20, more typically 1 to 10, still more typically 1 to 4, even more typically 1 to 2 and yet more typically 1; r is an integer from 1 to 4, more typically 1 or 2, still more typically 1; and Ar is optionally substituted aryl or optionally substituted aralkyl, provided that when one of X and Y is selected from C-NO$_2$, C-OH, C-Cl, C-CH$_3$ or C-NH$_2$ then the other X or Y substituent cannot be selected from C-NO$_2$, C-OH, C-Cl or C-NH$_2$. In moieties of formula $(CH_2)_pR^1$, $(CH_2)_pArR^1$, one or more methylene groups may also be replaced with O, S, NH or carbonyl, for example C(O)R^1, CH$_2$C(O)R^1, NHCH$_2$R^1, NHC(O)R^1, CH$_2$OR^1, CH$_2$C(O)NHR^1, and the like.

Typically in the compound of Formula (I), the functionalised linkage group Z of the compound of Formula (I) is selected from the group of halogen, maleimide, a vinyl pyridyl group of formula



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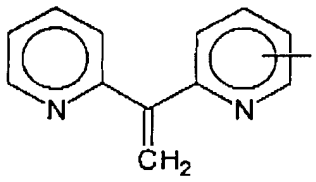
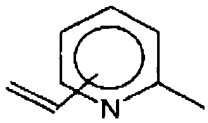
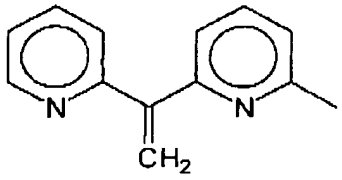


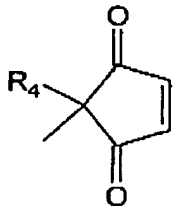


especially

or



or a dione of formula



NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $-(CH_2OCH_2O)_qArR^1$, $-(CHCH)_rR^1$, $(CHCH)_rArR^1$ and where R^1 is selected from NH_2, COOH, NCS, NCO, -N=N, or $-C(=NH)OCH_3$, COR" group where R" is H, halogen, alkyl, or alkyl substituted with a halogen or other leaving group, where p is an integer from 1 to 20, more typically 1 to 10, still more typically 1 to 4, even more typically 1 to 2 and yet more typically 1; q is an integer from 1 to 20, more typically 1 to 10, still more typically 1 to 4, even more typically 1 to 2 and yet more typically 1; r is an integer from 1 to 4, more typically 1 or 2, still more typically 1; and Ar is optionally substituted aryl or optionally substituted aralkyl, provided that at least one of R^2 and R^3 is other than hydrogen, and wherein, in moieties of formula $(CH_2)_pR^1$, $(CH_2)_pArR^1$, one or more methylene groups may also be replaced with O, S, NH or carbonyl, for example $C(O)R^1$, $CH_2C(O)R^1$, $NHCH_2R^1$, $NHC(O)R^1$, OR^1, SR^1, CH_2OR^1, $CH_2C(O)NHR^1$, and the like.

More typically in a compound of Formula (I), each R^4 and R^5 is H; W is NH; n is 2 to 4, more typically 2 or 3, still more typically 2; Z is selected from halogen and NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, provided that at least one of R^2 and R^3 is other than H; R^1 is

selected from NH_2, COOH, NCS, $NHCOCH_2Br$ and COR" where R" is halogen, typically Br; and p is an integer from 1 to 4, more typically 1 to 2 and still more typically 1. Yet more typically, R^1 is NH_2. Typically, R is amino, nitro, hydroxy or halogen and still more typically R is amino.

As used herein, the term "aryl" refers to single, polynuclear, conjugated and fused residues of aromatic hydrocarbons or aromatic heterocyclic ring systems. Examples of such groups are phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthracenyl, fluorenyl, pyrenyl, indenyl, azulenyl, chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrryl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolyl, isoquinolyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl, heteroaryl, pyridine and Het-$CH=CH_2$ and the like. Typically aryl is phenyl, pyridyl, naphthyl, anthracenyl or the like, and heteroaryl is typically pyridine and Het-$CH=CH_2$. Still more typically, aryl is phenyl.

As used herein, the term "aralkyl" refers to alkyl groups substituted with one or more aryl groups as previously defined. Examples of such groups are benzyl, 2-phenylethyl and 1-phenylethyl.

As used herein, the term "optionally substituted" means that the moiety described as optionally substituted may carry one or more substituents selected from amino, halogen, hydroxy, mercapto, nitro, cyano, thiocyano, alkyl, alkoxy, halogenoalkyl, acyl, acylamino, acyloxy, carboxyl, alkoxycarboxyl, carbamoyl, pyridoylamino, carboxyalkyl-carbamoyl, N-carboxyalkylcarbamoyl, sulpho, sulphamoyl, mono- or dialkylated or phenylated sulphamoyl which can carry one or more alkyl substituents, alkylsulphonyl, alkoxysulphonyl, optionally hydroxy-containing phenylsulphonyl or phenoxy sulphonyl.

In another form of the compound of Formula (I), the Z group of said compound of Formula (I) is selected from the group of NR^2R^3 where R^2 and R^3 together with the nitrogen atom to which they are attached form a substituted saturated or unsaturated 3 to 8 membered ring optionally containing one or more additional heteroatoms O, S or N and wherein there is at least one substituent capable of binding said compound of Formula (I) with a molecular recognition unit.

In accordance with a second embodiment of the present invention, there is also provided a compound of Formula (I) as described in the first embodiment of the present invention which is complexed with a metal ion.

The metal ion is typically selected from ^{64}Cu, ^{67}Cu, ^{99m}Tc, Ga, In, Co, Re, Fe, Au, Ag, Rh, Pt, Bi, Cr, W, Mo, Ni, V, Pb, Ir, Pt, Zn, Cd, Mn, Ru, Pd, Hg, Ti, Tl, Sn, Zr, and the lanthanide group of elements in the Periodic Table such as Sm, Ho, Gd, Tb, Sc, Y, and the actinides.

The metal ion is further typically a radionuclide selected from the group of ^{64}Cu, ^{67}Cu, ^{99m}Tc, and radionuclides of In(III), Ga (III), Fe (III), Cu (II), Ti (IV) and other radionuclides from the Lanthanides, Re, Sm, Ho, and Y.

In accordance with a third embodiment of the present invention, there is also provided a pharmaceutical formulation comprising a compound of Formula (I) as described in the first embodiment of the present invention or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

In accordance with a fourth embodiment of the present invention, there is also provided a diagnostic formulation comprising a compound of Formula (I) as described in the first embodiment of the present invention or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof and a reducing agent in a pharmaceutically acceptable carrier.

In accordance with a fifth embodiment of the present invention, there is also provided a method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a compound of Formula (I) as described in the first embodiment of the present invention or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof.

In accordance with a sixth embodiment of the present invention, there is also provided a use of a compound of Formula (I) or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof in the preparation of a medicament for diagnosis or therapy of disease in a subject.

In accordance with a seventh embodiment of the present invention, there is also provided a compound of Formula (I) as described in the first embodiment of the present invention or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof when used in the diagnosis or therapy of disease in a subject.

In accordance with an eighth embodiment of the present invention, there is also provided a conjugate compound comprising at least one compound of Formula (I) as described in the first embodiment of the present invention or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof bonded to at least one molecular recognition unit comprising an antibody, protein, peptide, carbohydrate, oligonucleotide, oligosaccharide, liposome or the like.

In accordance with a ninth embodiment of the present invention, there is provided a method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a conjugate compound as described in the eighth embodiment of the present invention.

In accordance with a tenth embodiment of the present invention, there is provided a use of a conjugate compound as described in the eighth embodiment of the present invention in the preparation of a medicament for diagnosis or therapy of disease in a subject.

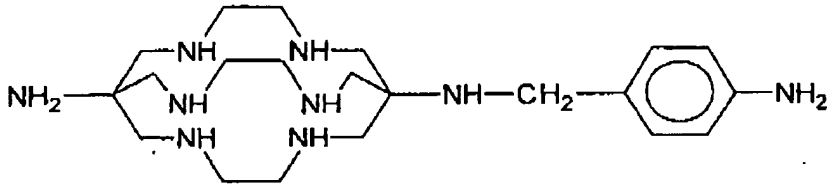
In accordance with an eleventh embodiment of the present invention, there is provided a conjugate compound as described in the eighth embodiment of the present invention when used in the diagnosis or therapy of disease in a subject.

In accordance with a twelfth embodiment of the present invention, there is provided a method of imaging a subject comprising introducing a compound of Formula (I) or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof to a subject.

In accordance with a thirteenth embodiment of the present invention, there is provided a use of a compound of Formula (I) or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof in the preparation of a medicament for imaging in a subject.

In accordance with a fourteenth embodiment of the present invention, there is provided a compound of Formula (I) or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof when used in imaging in a subject.

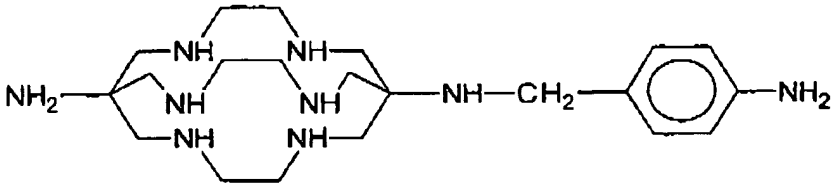
In accordance with a fifteenth embodiment of the present invention, there is provided a compound of Formula (I) having the following structure:



Detailed Description Of The Invention

The compounds of Formula (I) typically comprise those compounds where n represents an integer from 2 to 4, more typically 2 or 3, still more typically 2. Typically, one of X and Y is a C-Z group where Z is typically NR^2R^3 where R^2 and R^3 are the same or different and are selected from H, $(CH_2)_pR^1$ and $(CH_2)_pArR^1$, where R^1 is as previously defined, and p is 1 to 4, more typically 1 to 2 and still more typically 1, provided that at least one of R^2 and R^3 is other than hydrogen. Usually, one of X is a C-Z group and the other is a group C-R, where R is as previously defined, typically amino, lower alkyl, nitro, hydroxy or halogen. Generally, R^1 is NH_2 and p is 1.

An example of a compound of Formula (I) is:



The R^1 group in a compound of Formula (I) may provide a point of attachment of a compound of Formula (I) to a molecular recognition unit.

The molecular recognition unit is typically an antibody, protein, peptide, oligonucleotide, oligosaccharide. In particular, the molecular recognition unit is typically an antibody and more typically a monoclonal antibody.

Thus, compounds of Formula (I) provide a method of attachment of radionuclide metal ions such as In(III), Ga(III), Fe(III), Tc(IV) or Tc(V), Re(VII), Cu(II), Ti(IV), other radionuclides from the Lanthanides, Rhenium, Samarium, Holmium, Yttrium and the like to molecular recognition units such as monoclonal antibodies, receptor specific proteins, peptides or oligonucleotides for *in vivo* imaging and therapy.

The compounds of general Formula (I) are typically prepared by attachment of a functional linking group to a suitable cryptate. Methods of synthesis of cryptates useful as precursors to compounds of Formula (I) in which W is NH are described in United States Patent No. 4,497,737 in the name of Sargeson *et al*, the disclosure of which is incorporated herein by reference. Other cryptates where W is S or O may be prepared by analogous methods. Sargeson *et al* describe synthesis of metal cage "cryptate" compounds by the condensation of a tris-(diamine) metal ion complex as described at column 3 lines 30 to 35 with formaldehyde and an appropriate nucleophile. In order to obtain the compounds of Formula (I), an appropriate nucleophile is selected so as to obtain the desired functionalised linkage group Z as defined in Formula (I). In particular, reference is made to column 4 lines 17 to 27 of United States Patent No. 4,497,737. Alternatively, a functionalised linkage group Z may be attached to a functional group of a cryptate prepared by the methods taught by Sargeson *et al* (for example see Example 9 at column 9 line 65 to column 12 line 10 of Sargeson *et al*) by standard synthetic techniques. If necessary, a protecting group may be introduced into the cryptate structure to protect latent functionality for the desired functionalised linkage group Z as defined in Formula (I) during synthesis of the desired cryptate precursor. Suitable protecting groups are described, for example in Greene, T.W., *Protective Groups In Organic Synthesis* (John Wiley & Sons, New York, 1981) and McOmie, J.F.W., *Protective Groups in Organic Chemistry* (Plenum Press, London, 1973).

For example, compounds of Formula (I) where said Z group comprises a mono- or di-substituted amino group and where the substituent is optionally substituted alkyl, are readily prepared by treating the amino compound with the appropriate halo-substituted alkyl. Typically, the compound of Formula (I) where Z is $-NH-CH_2-CH_2-NH_2$ can be prepared by treating a compound of Formula (I) where R is NH_2 with $BrCH_2CH_2NH_2$ in the presence of $NaHCO_3$ or the like with suitable protection.

Compounds of formula (I) where R^1 is -NCS may be prepared by reacting the amino compound with thiophosgene (see WO87/12631), Kozak *et al.*, Cancer Res. 49, 2639 (1989). Substituted acid halide compounds are produced by reacting a compound of formula (I) where R is NH_2 with $BrCH_2COBr$ at 4°C according to the procedure of C J Mathias *et al.*, Bioconjugate Chem., 1, 204 (1990). Compounds with an electrophilic moiety can also be prepared by methods known in the art, such as in ACC Chem. Res. 17 202-209 (1984). Compounds with active esters $(CH)_p-C(O)-X$ may be formed by the procedures of Bodanszky M, *The Peptide. Analysis Synthesis Biology*, Ed. E. Gross and J Meienhofer, Vol 1. pp 105-196, Academic Press, Inc., Orlando, FL. (1979) and Bodanszky M, *Principles of Peptide Synthesis*, pp 9-58, Springerverlag, New York, (1984). Other compounds of

formula (I) may be prepared from such compounds by standard procedures such as described in Modern Synthetic Reactions, H O House, 2nd Edition, Benjamin. Inc. Philippines, 1972.

In a typical embodiment, compounds of formula (I) in which X or Y is C-Z where the group Z is a group $NH(CH_2)_pR^1$ or $NH(CH_2)_pArR^1$ may be prepared by a Schiff Base condensation reaction of a compound of formula (I) (or a metal complex thereof) in which X or Y is NH_2 with an aldehyde of formula $HC(O)(CH_2)_{p-1}R^1$ or $HC(O)(CH_2)_{p-1}ArR^1$. (Still typically, the Schiff Base condensation reaction is most appropriately conducted between a copper complex of compounds of Formula (I) in which X or Y is NH_2 with an aldehyde of formula $HC(O)(CH_2)_{p-1}R^1$ or $HC(O)(CH_2)_{p-1}R^1$.) In one particular form of this embodiment, a compound of formula (I) is obtained by the reaction of nitrobenzaldehyde with the copper complex of an aminocryptate such as described by Sargeson *et al.* The reaction is typically performed in an inert-gas atmosphere and in the presence of solvent and diluents typically inert to the reactants. Suitable solvents comprise aliphatic, aromatic, or halogenated hydrocarbons such as benzene, toluene, xylenes; chlorobenzene, chloroform, methylene chloride, ethylene chloride; ethers and ethereal compounds such as dialkyl ether, ethylene glycol mono or -dialkyl ether, THF, dioxane; alkanols such as methanol, ethanol, n-propanol, isopropanol; ketones such as acetone, methyl ethyl ketone; nitriles such as acetonitrile or 2-methoxypropionitrile; N,N-dialkylated amides such as dimethylformamide; dimethylsulphoxide, tetramethylurea; as well as mixtures of these solvents with each other. If the amine or a salt thereof is soluble in water, then the reaction medium may be water at low temperature. The compounds of formula (I) may be converted to pharmaceutically acceptable salts by way of recognised procedures.

Typically, for medical use salts of the compounds of the present invention will be pharmaceutically acceptable salts; although other salts may be used in the preparation of the inventive compound or of the pharmaceutically acceptable salt thereof. By pharmaceutically acceptable salt is meant those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art.

Suitable pharmaceutically acceptable salts of the compounds of the present invention may be prepared by mixing a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, phosphoric acid, acetic acid, oxalic acid, carbonic acid, tartaric acid, or citric acid. Suitable pharmaceutically acceptable salts of the compounds of the present invention therefore include acid addition salts.

For example, S. M. Berge *et al.* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences,* 1977, *66*:1-19. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Representative acid addition salts

include acetate, adipate, alginate, ascorbate, asparate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphersulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like.

The radiolabelling of compounds of formula (I), and salts thereof can be accomplished by using procedures recognised in the art. For example, radiolabelling of the chelator with ^{67}Cu can be achieved by adding copper in an aqueous acetate solution to a compound of formula (I) in an aqueous solution and incubating at room temperature.

Alternatively, the radiolabelling of a compound of formula (I) with technetium, for example, may be achieved by adding a reducing agent such as stannous salts typically stannous chloride, to an aqueous solution of a compound of formula (I), followed by reaction with aqueous sodium pertechnetate solution ($Na^{99m}TcO_4$). The order of mixing these three components is believed not to be critical. However, typically the reducing agent is added to the chelator of formula (I). Other suitable reducing agents comprise alkali metal dithionites such as sodium dithionite, sodium borohydride, hydrochloric acid, hydrobromic acid, other soluble dithionites such as potassium dithionite or ammonium dithionite, a soluble bisulfite or metabisulfite such as sodium bisulfite, potassium bisulfite, lithium bisulfite, ammonium bisulfite, sodium metabisulfite, potassium metabisulfite, lithium metabisulfite or ammonium metabisulfite, or an aqueous solution of sulfur dioxide.

Technetium-99m in the form of an aqueous solution of sodium pertechnetate is readily obtainable from commercially available molybdenum-99/technetium-99m generators or alternatively, instant ^{99m}Tc may be used. Cu-64 is commercially available from Australian Nuclear Science & Technology Organisation and ^{67}Cu from the US Department of Energy, Brookhaven, USA.

The conjugate compounds of the eighth embodiment of this invention may be formed by the reaction of a radiolabelled metal complex of a compound of Formula (I) together with a molecular recognition unit. The radionuclides which are useful for complexing with the compounds of Formula (I) typically comprise metal ions which have at least two oxidation states, most typically an oxidation state of +2 or +3. In a typical embodiment, the radiolabelled metal complex is selected from ^{64}Cu, ^{67}Cu and ^{99m}Tc, Sm, Ho, Re, Sc, Cu, Pd, Rh, and Y. The most typical metal ions comprise ^{64}Cu, ^{67}Cu, ^{99m}Tc.

These radiolabelled metal complexes are then reacted with a molecular recognition unit. The radiolabelled molecular recognition unit so formed is useful for diagnostic, therapeutic and radioimaging applications.

Alternatively a conjugate of a compound of formula (I) may be first prepared, and then it may be radiolabelled.

Thus, radiolabelling of molecular recognition units such as proteinaceous materials using compounds of formula (I) can be conducted in two ways, namely:

(a) prelabelling of a compound of Formula (I) with a suitable radionuclide, followed by conjugation of the resultant radiocomplexed compound to proteinaceous or other material, or

(b) conjugating the compound of formula (I) to proteinaceous or other material for subsequent radiolabelling.

The formation of a conjugate compound of formula (I) is usually achieved by the reaction of the functionalised linkage group with a thiol, amino, carboxyl, hydroxyl, aldehyde, aromatic or heteroaromatic group present in the molecular recognition unit. For example, an amino or hydroxy group of the functionalised linkage group may be reacted with a free carboxyl group of the molecular recognition unit, or vice versa. Suitably a coupling agent such as a carbodiimide may be employed to facilitate the coupling reaction.

The conjugate compounds according to the eighth embodiment of the present invention may contain more than one molecule of a compound of formula (I) to any one molecular recognition unit. The metal complexing and radiolabelling of compounds of formula (I), and pharmaceutically acceptable salts thereof can be accomplished by using procedures recognised in the art. For example, the radiolabelling of the conjugate compounds with ^{64}Cu may be achieved by adding an aqueous acetate solution of ^{64}Cu to the conjugate compound in an aqueous solution and incubating for 5 minutes at room temperature. A composition comprising an uncomplexed conjugate in accordance with the invention may also be supplied to radio-chemists, technicians, radiopharmacists, doctors or the like in the form of a kit for radiolabelling immediately prior to use.

In a typical form of this invention, the kit comprises a first container that contains a radiolabelling metal ion, usually in solution, and a second container that contains a conjugate compound as described in the eighth embodiment of the present invention. The kit, in use, then involves mixing the contents of said first and second containers to obtain the radiolabelled conjugate compound.

Typically, the compounds of Formula (I) or the metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof are useful for labelling molecular recognition units for use in methods of diagnosis and therapy of disease. In particular, the typical radiolabelled molecular recognition units are monoclonal antibodies and fragments thereof, peptides, oligonucleotides, oligosaccharides or liposome or a part of a specific binding pair.

The applications of radiolabelled molecular recognition units comprise diagnosis, imaging and therapy of disease such as cancer. Typically, the compounds of formula (I) and their metal complexes and/or salts thereof have a diagnostic use as imaging agents *in vitro* and *in vivo*. The method of diagnosis using the aforesaid imaging agents will result from the localisation of the radiolabelled conjugate compounds on specific organs and tissues in a subject.

The method of diagnosis will typically involve first the administration of an effective amount of a radiolabelled compound of Formula (I) to a subject; and then monitoring the subject after a suitable period of time in order to ascertain the presence or absence of a cancer for example as evidenced by localisation of the radiolabel at a particular site in the subject. Typically , the monitoring step shall provide information regarding the location of any cancer if it is present. The effective amount or dosage of the radiolabelled compound of Formula (I) will depend upon the desired amount of radioactivity required for the diagnostic application balanced with the safety requirement of not exposing the subject, in particular their organs and tissues, to harmful amounts of radiation. Appropriate dosages for any given application may be determined by persons skilled in the relevant art by no more than routine experimentation, given the teaching herein.

The method of therapy will typically involve compounds of formula (I) or the metal complexes, radiolabelled complexes and/or pharmaceutically acceptable salts thereof which are useful as cytotoxic agents. In a typical embodiment, the therapy of disease comprises treatment of cancer, abnormal cell disorders and the treatment of tumours. In such applications, the radiolabelled compound of formula (I) is typically conjugated to a molecular recognition unit which is capable of binding specifically to the tumour or abnormal cell. Examples of such molecular recognition units comprise one part of specific binding pairs and are known to persons skilled in the relevant art and typically comprise antibody/antigen pairs and the like.

The method of therapy will typically involve the administration of an effective amount of a radiolabelled compound of Formula (I) to a subject. The effective amount or dosage will depend upon the desired amount of radioactivity required for the diagnostic application balanced with the safety requirement of not exposing the subject, in particular their organs and tissues, to harmful amounts of radiation. Appropriate dosages for any given application may be determined by persons skilled in the relevant art by no more than routine experimentation, given the teaching herein.

Typically the treatment would be for the duration of the condition, and contact times would typically be for the duration of the condition.

Further, it will be apparent to one of ordinary skill in the art that the optimal quantity and spacing of individual dosages of a compound of the present invention will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the nature of the particular vertebrate being treated. Also, such optimum conditions can be determined by conventional techniques.

It will also be apparent to one of ordinary skill in the art that the optimal course of treatment, such as, the number of doses of the compound of the present invention given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

Also included within the scope of the present invention are prodrugs of the inventive compound. Typically, prodrugs will be functional derivatives of a compound of Formula (I) in accordance with the first embodiment of the invention, which are readily converted *in vivo* to the required compound for use in the present invention as described herein. Typical procedures for the selection and preparation of prodrugs are known to those of skill in the art and are described, for instance, in H. Bundgaard (Ed), *Design of Prodrugs*, Elsevier, 1985.

When used in the treatment of disease, the compound of Formula (I) in accordance with the first embodiment of the invention or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof, may be administered alone. However, it is generally preferable that these compounds be administered in conjunction with other chemotherapeutic treatments conventionally administered to patients for treating disease. For example, a tumour may be treated conventionally with surgery, and the compound of Formula (I) in accordance with the first embodiment of the invention or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof, to extend the dormancy of micrometastases and to stabilise and inhibit the growth of any residual primary tumour.

Typically, when used in the treatment of solid tumours, compounds of the present invention may be administered with chemotherapeutic agents such as: adriamycin, taxol, fluorouricil, melphalan, cisplatin, alpha interferon, COMP (cyclophosphamide, vincristine, methotrexate and prednisone), etoposide, mBACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone), PROMACE/MOPP (prednisone, methotrexate (w/leucovin rescue), doxorubicin, cyclophosphamide, taxol, etoposide/mechlorethamine, vincristine, prednisone and procarbazine), vincristine, vinblastine, angioinhibins, TNP-470, pentosan polysulfate, platelet factor 4, angiostatin, LM-609, SU-101, CM-101, Techgalan, thalidomide, SP-PG and the like. Other chemotherapeutic agents include alkylating agents such as nitrogen mustards including mechloethamine, melphan, chlorambucil, cyclophosphamide and ifosfamide; nitrosoureas including carmustine, lomustine, semustine and streptozocin; alkyl sulfonates including busulfan; triazines including dacarbazine; ethyenimines including thiotepa and hexamethylmelamine; folic acid analogues including methotrexate; pyrimidine analogues including 5-fluorouracil, cytosine arabinoside; purine analogues including 6-mercaptopurine and 6-thioguanine; antitumour antibiotics including actinomycin D; the anthracyclines including doxorubicin, bleomycin, mitomycin C and methramycin; hormones and hormone antagonists including tamoxifen and cortiosteroids and miscellaneous agents including cisplatin and brequinar.

When used in the treatment of disease, the compound of Formula (I) in accordance with the first embodiment of the invention or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof, may be administered alone. However, it is generally preferable that they be administered as pharmaceutical formulations. In general pharmaceutical formulations of the present invention may be prepared according to methods which are known to those of ordinary skill in the art and accordingly may include a pharmaceutically acceptable carrier, diluent and/or adjuvant.

These formulations can be administered by standard routes. In general, the combinations may be administered by the topical, transdermal, intraperitoneal, intracranial, intracerebroventricular, intracerebral, intravaginal, intrauterine, oral, rectal or parenteral (e.g., intravenous, intraspinal, subcutaneous or intramuscular) route. In addition, the compound of Formula (I) in accordance with the first embodiment of the invention or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof, may be incorporated into biodegradable polymers allowing for sustained release, the polymers being implanted in the vicinity of where drug delivery is desired, for example, at the site of for example, a tumour or implanted so that the active agents are slowly released systemically. Osmotic minipumps may also be used to provide controlled delivery of high concentrations of the active agents through cannulae to the site of interest, such as directly into for example, a metastatic growth or into the vascular supply to that tumour.

The carriers, diluents and adjuvants must be "acceptable" in terms of being compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

Examples of pharmaceutically and veterinarily acceptable carriers or diluents are demineralised or distilled water; saline solution; vegetable based oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oils such as peanut oil, safflower oil, olive oil, cottonseed oil, maize oil, sesame oil, arachis oil or coconut oil; silicone oils, including polysiloxanes, such as methyl polysiloxane, phenyl polysiloxane and methylphenyl polysolpoxane; volatile silicones; mineral oils such as liquid paraffin, soft paraffin or squalane; cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxymethylcellulose, sodium carboxymethylcellulose or hydroxypropylmethylcellulose; lower alkanols, for example ethanol or iso-propanol; lower aralkanols; lower polyalkylene glycols or lower alkylene glycols, for example polyethylene glycol, polypropylene glycol, ethylene glycol, propylene glycol, 1,3-butylene glycol or glycerin; fatty acid esters such as isopropyl palmitate, isopropyl myristate or ethyl oleate; polyvinylpyrridone; agar; carrageenan; gum tragacanth or gum acacia, and petroleum jelly. Typically, the carrier or carriers will form from 10% to 99.9% by weight of the compositions.

For administration as an injectable solution or suspension, non-toxic parenterally acceptable diluents or carriers can include, Ringer's solution, isotonic saline, phosphate buffered saline, ethanol and 1,2 propylene glycol.

Adjuvants typically include emollients, emulsifiers, thickening agents, preservatives, bactericides and buffering agents.

Methods for preparing parenterally administrable compositions are apparent to those skilled in the art, and are described in more detail in, for example, Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa., hereby incorporated by reference herein.

The radiolabelled molecular recognition units especially radiolabelled antibodies are particularly useful in medicine, for example, in locating specific tissue types and in the therapy of cell disorders. The radiolabelled antibodies can also be used to target metal ions to a specific tissue type, both *in vitro* and *in vivo*.

A typical use of the radiolabelled compounds of Formula (I) is to radiolabel monoclonal antibodies specific for colon, ovarian, lymphoma, breast and/or bladder cancer, with beta emitter radionuclides of metals such as Sm, Ho, Re, Sc, Cu, Pd, Pb, Rh and Y for therapy of above mentioned cancer. A further typical use is in the radiolabelling of a monoclonal antibody specific for metastasis of colon cancer for diagnosis and therapy.

In another typical embodiment, the antibody in the conjugate compound may be a complete antibody molecule or a fragment thereof or an analogue of either of these, provided that the antibody comprises a specific binding region. The antibody may be a humanised monoclonal or a fragment thereof. The antibody may also be a recombinant antibody. The antibody may be specific for any number of antigenic determinants, but is typically specific for one antigenic determinant.

In another typical embodiment, there is provided radiolabelling of monoclonal antibodies with ^{67}Cu (beta and gamma emitter) and ^{64}Cu (positron and beta emitter), for combined radioimmunoscintography (RIS) (SPECT and PET) and radioimmunotherapy (RIT). Other radionuclides comprise Auger emitting agents where the compound of Formula (I) is coupled to the monoclonal antibody and labelled with auger emitting isotope such as Fe-59 or Cu-64.

In still another typical embodiment, there is provided a two step pretargeted radioimmunotherapy where a monoclonal antibody with a first marker molecule attached thereto is injected into a subject. Once the antibody has cleared from the system and localised to the tumour, a second injection is administered to the subject. This second injection typically involves the radiolabelled complex of Formula (I) attached to a second marker molecule which recognises the first marker molecule on the targeted antibody. Alternatively, the second injection may typically be the second marker molecule alone and when cleared from the system, the radiolabelled complex of Formula (I) attached to the first marker molecule is administered to the subject. Both procedures provide amplification of the target site and reduce exposure of the radiolabelled complex to normal tissue. Still typically, the first marker molecule is biotin and the second marker molecule is avidin or streptavidin. Still more typically, the first marker molecule is smaller than the targeted antibody.

The invention also provides a two step procedure which involves the administration of an antibody-DNA conjugate or antibody-oligonucleotide conjugate followed by targeting with a radiolabelled complementary DNA or complementary oligonucleotide. This procedure also provides amplification of the target site and reduces exposure complex of the radiolabelled to normal tissue.

The invention also provides a use of compounds of Formula (I) or metal complexes, radiolabelled complexes, conjugate compounds or pharmaceutically acceptable salts thereof as Magnetic Resonance Imaging (MRI) agents. In this form of the invention, there is typically formed a complex of compound of formula (I) or a conjugate of the eighth embodiment, with a paramagnetic metal ion, typically Fe (III), Mn(II), which may be used as a contrast agent to enhance images. Further, complexes such as these may be employed in the form of a pharmaceutical formulation where the complex is present with a pharmaceutically acceptable carrier, excipient or vehicle therefor.

The pharmaceutical formulations described for the different embodiments of this invention typically comprise a formulation in the form of a suspension, solution or other suitable formulation. Physiologically acceptable suspending media together with or without adjuvants may be used. Still typically, the pharmaceutical formulations are in a liquid form and still more typically are in an injectable form. Still more typically, the injectable formulations are dissolved in suitable physiologically acceptable carriers which are recognised in the art.

The industrial use of the compounds of formula (I) further comprises their attachment to solid surfaces such as polymers, for use in the concentration of metal ions and purification of water or attached to an electrode surface for detection of specific metal ions.

Brief Description Of The Drawings

The present invention will be further illustrated, by way of example only, with reference to the accompanying figures; in which:

Figures 1a and 1b are graphical representations of the serum stability of ^{67}Cu complex of compound (4) at 0 and 7 days respectively;

Figure 2 is a graphical representation of the effect of pH on the complexation of ^{64}Cu with compound (3);

Figure 3 is a graphical representation of the biodistribution of a ^{64}Cu complex of compound (4);

Figure 4 is a graphical representation of the biodistribution of a ^{64}Cu complex of compound (1);

Figure 5 is a graphical representation of the biodistribution of a ^{64}Cu complex of compound (3); and

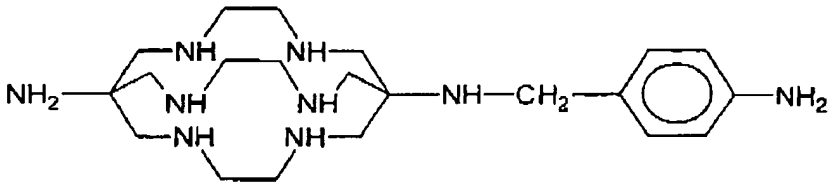
Figure 6 is a graphical representation of the biodistribution of ^{64}Cu labelled conjugate of B72.3 conjugated with compound (3) in Tumour Bearing Nude Mice.

Figure 7 is a graphical representation of the radiotherapeutic effect of 30MBq of ^{64}Cu labelled conjugate of B72.3 conjugated with compound (3) in Tumour Bearing Nude Mice.

Examples

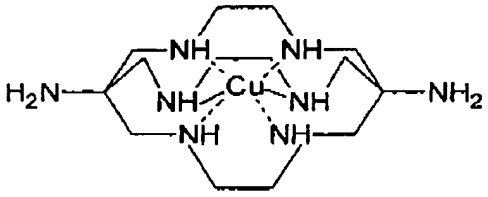
The following examples serve only to illustrate the invention and should not be construed as limiting the generality of the above description.

Example 1: Preparation of Compound (3)

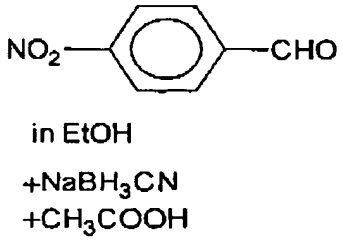


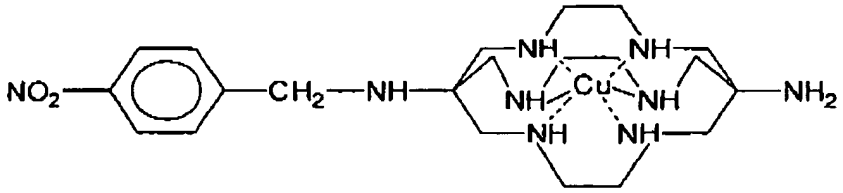
Compound (3)

Preparation of compound (3) is illustrated in Schemes 1 and 2.



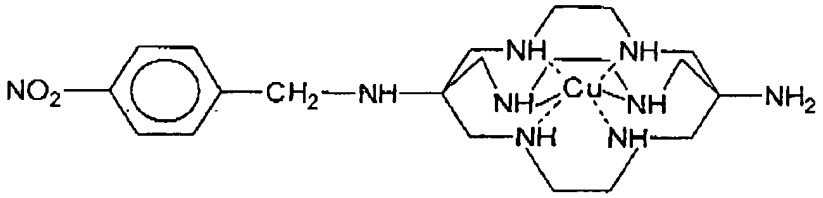
[1]



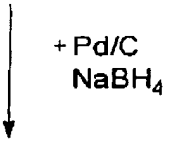


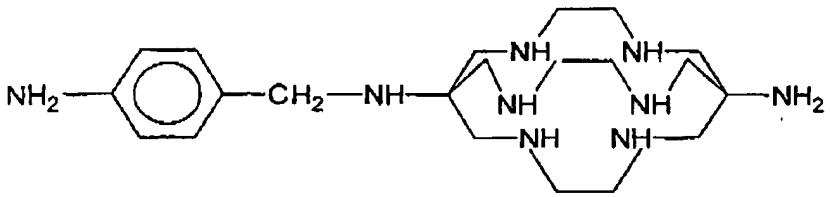
[2]

Scheme 1. Schiff Base Condensation reaction of compound (1) with p-nitrobenzaldehyde



[2]





[3]

Scheme 2. Reduction of compound (2) to compound (3).

A. Preparation of Compound (2)

Compound (2) is prepared by Schiff base reaction of compound (1) with p-nitrobenzaldehyde. Synthesis of compound (1) is described in *Aust. J. Chem* (1994) 47, 143–179. A copper complex of (1) is dissolved in dry ethanol (2.4 mmoles in 100 mls) and p-nitrobenzaldehyde (2.2 mmoles) is added. The reaction mixture is evaporated to dryness and reconstituted (with dry ethanol) twice to remove any water. The reaction mixture is once again reconstituted in dry ethanol and stirred for 30 mins under nitrogen gas. Sodium cyanoborohydride (25 mmoles), glacial acetic acid (2 mmoles) and activated 3 Å molecular sieves are added and the reaction is allowed to stir overnight. The mixture is filtered, evaporated to dryness and extracted with chloroform and water (100 ml : 200 ml). The water layer is diluted to 2 L, sorbed onto SP Sephadex C25 and eluted with 0.3 M sodium acetate. (Scheme 1).

B. Preparation of Compound (3)

To palladium/C catalyst (20 mg) in water (0.5 ml) is added sodium borohydride (50 mg) in water (0.5 ml) under nitrogen gas. To this mixture is then added compound (2) (30 mg) dissolved in approximately 0.1 M sodium hydroxide (0.5 ml). The mixture is left to stir at room temperature for a further 30 mins or until the solution becomes clear. A 2 ml glass vial is cooled on ice. The mixture is 0.22 µm filtered into the cooled vial to remove the suspended palladium/C catalyst. To this cooled filtrate is added concentrated hydrochloric acid dropwise until all excess sodium borohydride is quenched (i.e. until gas evolution on addition of acid ceases). The quantity of product is determined by titration with a known concentration of ^{64}Cu as described in Example 2. Product is stored frozen at pH < 1 in a rubber-stoppered vial under nitrogen gas. Yield: > 95% (Scheme 2). The final product is characterised by ^1H-NMR in D_2O at 298K (Bruker Avance DPX 400). ^1H NMR 3.28 ppm, m, 6H, CH_2 (cage); 3.39 ppm, m, 6H, CH_2 (cage); 3.59 ppm, s, 6H, CH_2 (cage); 3.71 ppm, s, 6H, CH_2 (cage); 4.45 ppm, s, 2H, CH_2; 7.51 ppm, d, 2H, Ar; 7.70 ppm, d, 2H, Ar.

Example 2 Complexation of ^{64}Cu by Compound (3)

The effect of pH on complexation of ^{64}Cu by compound (3) was investigated. Compound (3) was diluted into buffers of pH 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0. A sufficient amount of ^{64}Cu was added and the rate of complexation was monitored at (t = 1, 2.5, 5, 10, 60 and 90 mins) (see method below) by Instant Thin Layer Chromatography (ITLC-SG). Complete complexation (> 98 %) was achieved within 1 min for all pH ≥ 4.0. The rate of complexation at pH 3.0 was slower. (Figure 2).

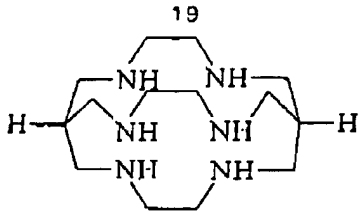
Monitoring Complexation by ITLC-SG

ITLC-SG strips (10 cm X 0.8 cm) were spotted with ~ 1 µL of reaction mixture 1 cm from the bottom of the strip (origin) and were developed in a solvent containing 0.1 M sodium acetate (pH 4.5) : ethanol = 9:1. ^{64}Cu-compound (3) remains at the origin ($R_f = 0.0$), and "free" ^{64}Cu appears at the solvent front ($R_f = 1.0$).

A typical method of radiolabelling the ligand is achieved by adjusting the pH of an aqueous solution of the ligand to pH 5.0. Sufficient volume of $^{64/67}Cu$ solution (usually in 0.02 M HCl or diluted into 0.1 M sodium acetate buffer pH 5.0) is added to form a 1:1 complex. The efficacy of labelling is determined by ITLC-SG as described above. One main radiochemical species is observed.

Example 3 Serum Stability of ^{67}Cu complex of compound (4)

Serum stability studies were conducted by incubating a ^{67}Cu complex of related species (4) in human plasma at 37°C.



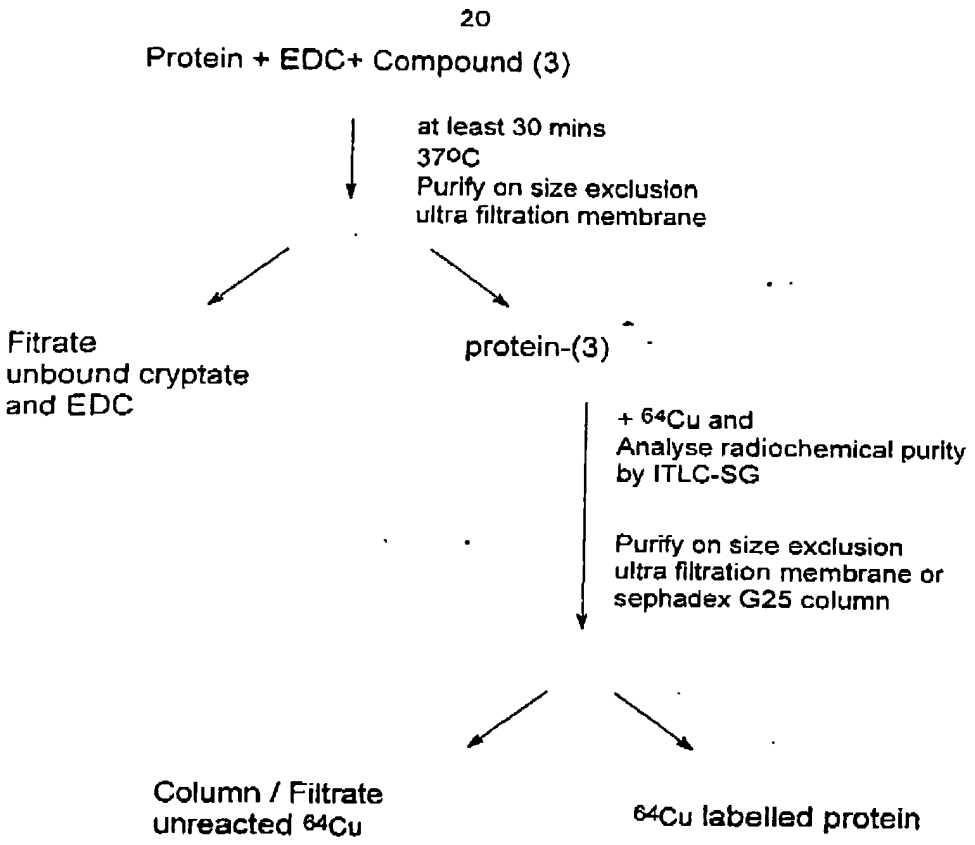
[4]

At various time intervals, the complex was separated from the plasma by size exclusion chromatography and the complex breakdown was assessed. Results indicated that no more than 2% of the copper is lost from the chelator during the first 174 hours at 37°C. (Figure 1a and 1b)

Example 4 Synthesis of B72.3 conjugated with (3) using 1-Ethyl-3-(3-dimethylamino-propyl)carbodiimide (EDC)

A typical method for radiolabelling an antibody (such as B72.3) is to incubate the antibody with the ligand (such as compound (3)) in the presence of EDC at pH 5.0 for 30 mins at 37°C. The unreacted ligand and EDC by-products are removed by washing with buffer (pH 5.0) on a size exclusion ultra filtration membrane. The purified immunoconjugate is exposed to a slight excess of $^{64/67}Cu$. The reaction is allowed to proceed at room temperature, and labelling is complete in less than 5 mins. Excess $^{64/67}Cu$ is removed by washing with 0.1 M EDTA in PBS (pH 7.2) on a size exclusion ultra filtration membrane or by separation on a size exclusion column (sephadex G25, eluted with PBS pH 7.2). (Scheme 3)

The conditions for radiolabelling B72.3 were optimised over incubation time (30 mins), reaction pH (5.0), concentration of B72.3 (5 mg/ml) and the molar ratio of B72.3:EDC:ligand (1:1000:250).



Scheme 3. Synthesis of protein conjugated with compound (3) using EDC.

Example 5 Biodistribution of Cu complexes of (1), (3) and (4) in Balb/C mice

The biodistribution of the ^{64}Cu complexes of compounds (1), (3) and (4) (0.10 ml intravenous injection) were evaluated in balb/c mice (5 animals per time point) at 3, 5, 10, 15, 20 and 30 minute time intervals. Biodistribution studies were performed in duplicate. Biodistribution of the radiolabel is presented in Tables 1, 2 and 3, and is illustrated diagrammatically in Figures 3, 4 and 5.

Example 6 Evaluation of ^{64}Cu-labelled conjugate of B72.3 with compound (3) in Tumour Bearing Nude mice

The B72.3 antibody recognises the TAG-72 antigen which is expressed on colorectal and ovarian tumours. The animal model used in the present study uses LS174t cells which also express TAG-72 antigen. The biodistribution of the ^{64}Cu immunoconjugate (0.10 ml intravenous injection) was evaluated in LS174t tumour bearing nude mice (5 animals per time point) at 1, 3, 5, 24 and 48 hour time intervals. Biodistribution studies were performed in duplicate. Biodistribution of the radiolabel is presented in Table 4, and is illustrated diagrammatically in Figure 6a; Biodistribution of complex of compounds (1) (2) and (3) show that if the ligand actually detaches from the antibody in any form it will clear rapidly from the system and not release the ^{64}Cu.

TABLE 1.

^{64}Cu-labelled compound (4)

% INJECTED DOSE PER GRAM

TIME	3 MIN		5 MIN		10 MIN		15 MIN		20 MIN		30 MIN	
ORGAN	MEAN	S.D.	MEAN	S.D	MEAN	S.D	MEAN	S.D	MEAN	S.D	MEAN	S.D
LIVER	1.81	0.30	1.59	0.12	1.16	0.06	0.64	0.06	5.01	0.55	5.76	0.58
SPLEEN	2.26	0.43	2.17	0.29	1.28	0.14	0.67	0.15	0.52	0.08	0.35	0.07
KIDNEY	20.08	4.98	18.62	4.09	14.79	6.26	7.52	0.54	25.99	3.24	30.26	4.50
MUSCLE	1.76	0.23	2.10	0.59	1.24	0.27	1.73	1.32	0.36	0.06	1.27	1.43
SKIN	5.98	0.31	6.46	0.56	4.21	0.68	2.76	0.10	1.73	0.45	1.42	0.42
BONE	1.60	0.25	1.56	0.24	1.28	0.23	1.60	0.41	0.89	0.51	0.65	0.10
LUNGS	5.85	0.03	5.28	0.46	2.84	1.09	2.09	0.24	1.13	0.30	0.92	0.15
HEART	3.25	0.34	2.66	0.14	1.60	0.36	1.08	0.18	0.51	0.08	0.47	0.17
BLOOD	8.25	0.32	7.08	0.22	4.41	0.78	2.71	0.57	1.40	0.12	1.07	0.21
BLADDER	13.15	6.81	28.05	18.33	69.91	54.03	8.17	4.96	16.38	20.77	25.38	35.78
STOMACH	3.53	0.56	3.04	0.29	1.84	0.55	0.89	0.37	0.70	0.14	0.65	0.10
GIT	2.62	0.08	2.16	0.20	1.49	0.31	1.07	0.18	0.89	0.05	0.80	0.04

TABLE 2.

^{64}Cu-labelled compound (1)

% INJECTED DOSE PER GRAM

TIME	3 MIN		5 MIN		10 MIN		15 MIN		20 MIN		30 MIN	
ORGAN	MEAN	S.D.	MEAN	S.D	MEAN	S.D	MEAN	S.D	MEAN	S.D	MEAN	S.D
LIVER	2.29	0.22	1.50	0.17	1.42	0.22	0.82	0.19	0.69	0.15	0.50	0.08
SPLEEN	2.09	0.52	1.48	0.21	1.54	0.25	1.44	0.76	0.69	0.12	0.52	0.16
KIDNEY	23.18	11.73	11.50	1.34	12.80	1.83	6.77	1.40	7.77	0.67	4.95	0.92
MUSCLE	1.81	0.32	1.81	0.59	2.39	1.14	2.28	1.66	1.17	1.02	1.33	1.59
SKIN	5.82	0.42	5.59	0.59	5.48	1.07	2.61	0.44	2.96	0.72	1.63	0.08
BONE	2.25	0.45	1.87	0.47	1.79	0.29	1.23	0.12	1.25	0.44	0.78	0.23
LUNGS	6.51	1.28	4.45	0.54	3.91	1.98	2.06	0.32	2.73	0.61	0.85	0.31
HEART	3.11	0.38	2.25	0.10	2.27	0.43	0.89	0.12	1.23	0.71	0.40	0.10
BLOOD	8.68	1.35	6.32	0.70	5.45	0.81	2.48	0.31	2.63	0.29	1.14	0.25
BLADDER	24.36	16.90	31.12	19.21	27.75	21.59	15.17	8.53	23.29	15.56	122.93	71.11
STOMACH	3.50	0.64	2.73	0.36	2.08	0.80	1.50	0.46	1.16	0.06	0.74	0.04
GIT	2.75	0.59	2.21	0.08	1.85	0.38	1.11	0.06	1.05	0.17	1.16	0.72

TABLE 3.

^{64}Cu-labelled compound (3)

% INJECTED DOSE PER GRAM

TIME	3 MIN		5 MIN		10 MIN		15 MIN		20 MIN		30 MIN	
ORGAN	MEAN	S.D.	MEAN	S.D	MEAN	S.D	MEAN	S.D	MEAN	S.D	MEAN	S.D
LIVER	1.94	0.17	2.00	0.52	1.46	0.39	1.24	0.23	1.04	0.08	0.72	0.02
SPLEEN	1.96	0.14	2.01	0.16	1.26	0.20	1.09	0.25	0.93	0.13	0.39	0.05
KIDNEY	22.41	5.77	18.99	2.98	13.41	3.04	10.26	1.76	9.98	1.73	5.95	0.27
MUSCLE	1.98	0.48	3.17	2.34	1.73	0.28	2.40	1.39	2.13	1.35	0.50	0.01
SKIN	5.63	1.05	6.18	1.17	4.86	1.14	4.49	1.03	3.41	1.10	1.45	0.13
BONE	1.68	0.04	2.11	0.60	1.29	0.43	1.36	0.24	1.11	0.08	0.72	0.10
LUNGS	5.48	0.61	5.74	1.07	4.00	0.79	3.25	0.64	2.59	0.50	1.13	0.01
HEART	2.79	0.36	3.00	0.59	2.03	0.58	1.56	0.29	1.24	0.05	0.50	0.11
BLOOD	7.74	0.43	8.19	1.53	5.23	1.28	4.39	0.59	3.05	0.44	1.25	0.02
BLADDER	11.36	4.02	12.31	4.09	14.36	9.79	10.54	9.64	13.45	16.47	2.74	2.02
STOMACH	2.69	0.51	3.11	0.79	2.35	0.65	1.91	0.45	1.54	0.33	0.60	0.04
GIT	2.66	0.29	2.88	0.46	1.80	0.38	2.92	2.46	1.05	0.22	0.55	0.03

TABLE 4.

^{64}Cu-labelled conjugate of B72.3 with compound (3)

	% INJECTED DOSE PER GRAM											
TIME	1 HR		3 HR		5 HR		16 HR		24 HR		48 HR	
ORGAN	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
LIVER	19.09	1.05	18.44	0.58	19.54	2.34	16.38	1.59	15.52	2.95	13.76	3.21
SPLEEN	11.51	1.13	8.35	1.19	10.17	0.98	10.08	1.75	8.47	1.89	8.44	1.57
KIDNEY	10.64	1.47	9.94	0.15	10.41	1.10	9.16	1.77	7.39	0.65	7.59	1.35
MUSCLE	1.45	0.52	1.48	0.23	1.45	0.16	1.98	0.27	2.54	0.54	1.72	0.42
SKIN	2.83	0.52	5.18	0.26	5.99	1.38	8.64	1.16	8.30	1.30	6.95	0.16
BONE	4.42	0.55	3.82	0.49	3.21	0.30	3.93	0.49	4.28	0.72	3.39	0.38
LUNGS	13.32	1.52	11.43	1.44	9.78	0.86	11.03	1.93	7.76	0.87	6.81	1.09
HEART	10.56	2.29	8.58	1.21	9.04	3.30	6.77	0.92	5.14	0.72	5.20	0.43
BLOOD	47.98	5.60	37.94	1.52	33.41	3.66	26.41	1.48	21.50	1.81	18.69	2.01
BLADDER	2.33	0.77	2.93	0.62	3.15	0.47	7.00	5.09	5.41	2.37	4.87	0.92
STOMACH	1.41	0.29	1.69	0.33	2.32	0.51	1.48	0.74	1.58	0.31	1.43	0.32
GIT	2.23	0.35	2.60	0.20	2.87	0.23	2.28	0.14	2.20	0.20	1.86	0.31
TAIL	5.03	0.73	4.96	0.83	5.64	1.82	6.14	2.47	5.18	1.20	4.08	0.30
TUMOUR	5.98	0.80	11.10	0.76	12.31	1.68	23.77	2.46	29.43	4.44	38.43	4.79

Table 5

Biodistribution of ^{131}I-B72.3 in nu/nu mice

% ID/g Time (hours) ORGAN	1 Mean	SD	3 Mean	SD	6 Mean	SD	16 Mean	SD	24 Mean	SD	48 Mean	SD
LIVER	11.89	2.33	8.93	1.24	7.45	1.51	5.61	0.64	5.03	0.82	4.92	0.90
SPLEEN	10.17	2.79	6.92	0.92	6.27	0.79	5.20	0.95	4.33	1.34	4.58	1.25
KIDNEY	11.20	0.77	8.89	1.40	9.24	0.53	5.83	0.88	5.40	0.98	4.76	0.78
MUSCLE	1.69	0.42	2.40	0.43	3.04	0.59	2.55	0.65	2.70	0.42	2.48	0.33
SKIN	4.36	1.85	5.96	0.94	7.79	0.76	7.94	0.95	7.96	0.78	7.41	1.44
BONE	5.43	0.54	4.43	0.69	3.23	0.43	3.19	0.78	2.58	0.58	2.54	0.36
LUNGS	14.28	2.97	12.84	2.89	11.00	1.57	7.39	1.62	6.64	1.57	6.47	0.64
HEART	14.03	6.26	10.11	1.16	9.46	1.59	7.28	2.50	5.78	0.62	4.87	1.10
BLOOD	55.63	3.36	44.78	4.03	42.20	3.93	28.27	3.00	28.73	2.23	22.73	2.50
URINE	3.96	0.58	13.29	5.00	18.31	6.92	7.28	4.17	6.92	1.11	6.87	2.11
BLADDER	3.49	1.15	5.10	1.63	4.85	0.91	4.74	1.24	5.70	1.13	6.63	1.23
STOMACH	1.80	0.23	2.94	0.44	4.06	0.50	2.64	0.90	3.06	0.99	3.05	0.72
GIT	2.35	0.26	2.74	0.29	2.74	0.39	1.84	0.33	1.65	0.26	1.51	0.07
THYROID	8.76	3.60	17.29	6.24	38.66	7.92	29.47	9.54	85.96	44.73	549.83	353.44
TUMOUR	9.61	2.04	16.46	1.61	31.43	8.39	31.37	6.54	44.67	8.50	46.17	7.25
%ID THYROID	0.08	0.02	0.19	0.03	0.42	0.11	0.40	0.18	1.24	0.64	2.59	1.13
TUMOUR:BLOOD	0.2	0.0	0.4	0.1	0.7	0.3	1.1	0.3	1.6	0.4	2.0	0.5
TUMOUR:LIVER	0.8	0.3	1.8	0.4	4.2	2.0	5.6	1.8	8.9	3.1	9.4	3.2
TUMOUR:KIDNEY	0.9	0.2	1.9	0.5	3.4	1.1	5.4	1.9	8.3	3.1	9.7	3.1
KIDNEY:BLOOD	0.2	0.0	0.2	0.0	0.2	0.0	0.2	0.1	0.2	0.0	0.2	0.1
KIDNEY:LIVER	0.9	0.2	1.0	0.3	1.2	0.3	1.0	0.3	1.1	0.4	1.0	0.3

Table 6.

Biodistribution of ^{111}In-DTPA-B72.3 in nu/nu mice.

% ID/g												
Time (hours)	1		3		6		16		24		48	
ORGAN	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
LIVER	13.4	1.72	10.54	1.41	11.2	1.2	7.27	0.86	8.43	2.28	7.59	0.72
SPLEEN	12.52	2.66	9.56	1.96	10.05	2.55	6.47	3.33	7.32	1.43	4.48	2.28
KIDNEY	15.41	1.57	12.04	1.67	14.13	1.83	15.59	1.39	13.97	1.64	15.04	1.57
MUSCLE	2.08	0.81	1.96	0.42	2.56	0.32	2.44	0.82	2.28	0.26	1.84	0.51
SKIN	4.17	1.98	7.54	1.53	9.31	1.41	9.48	1.21	8.44	0.42	7.54	0.75
BONE	5.9	1.12	4.59	0.53	3.85	0.97	5.81	1.12	5.52	0.58	5.23	0.9
LUNGS	18.58	4.72	13.14	4.58	13.03	2.65	8.06	1.89	6.58	1.4	7.07	1.93
HEART	11.9	3.88	9.59	1.65	11.71	4.12	6.25	0.88	4.99	0.39	3.95	0.45
BLOOD	56.19	9.04	39.03	4.66	38.23	3.64	26.51	1.72	21.78	2.36	17.04	0.89
URINE			5.23	0	3.96	1.16	4.46	1.68	4.46	1.12	4.43	1.56
BLADDER	11.82	9.4	5.59	2.85	8.31	19.94	7.68	2.97	6.88	1.87	4.28	0.39
STOMACH	2.43	0.8	2.49	0.66	2.2	0.9	1.53	0.48	1.47	0.46	1.47	0.44
GIT	2.12	0.34	2.44	0.51	2.33	0.42	2.17	0.25	2.04	0.2	2.33	0.2
TAIL	9.37	5.68	8.39	4.38	8.53	5.27	4.98	1.17	4.69	0.96	3.79	1.37
THYRIOD	18.66	8.1	25.91	17.2	8.09	3.14	7.37	1.62	8.51	2.21	4.45	0.91
TUMOUR	8.87	2.39	17.95	4.93	21.24	6.11	38.25	8.71	35	5.21	48.99	4
%ID THYROID	0.07	0.01	0.06	0.03	0.07	0.01	0.07	0.02	0.06	0.03	0.06	0.01
TUMOUR:BLOOD	0.2	0.1	0.5	0.2	0.6	0.2	1.4	0.4	1.6	0.4	2.9	0.4
TUMOUR:LIVER	0.7	0.3	1.7	0.7	1.9	0.7	5.3	1.8	4.2	1.7	6.5	1.1
TUMOUR:KIDNEY	0.6	0.2	1.5	0.6	1.5	0.6	2.5	0.8	2.5	0.7	3.3	0.6
KIDNEY:BLOOD	0.3	0.1	0.3	0.1	0.4	0.1	0.6	0.1	0.6	0.1	0.9	0.1
KIDNEY:LIVER	1.2	0.3	1.1	0.3	1.3	0.3	2.1	0.4	1.7	0.6	2.0	0.4

It is to be understood that the term "SarAr" as used in the following tables and description refers to compound (3) as shown in example 1.

Table 7 Maximum Radiation Dose Estimates for ^{64}Cu-SarAr-B72.3

Organ	Total Dose mGy/MBq	Total Dose Rad/mCi
Adrenals	0.030	0.111
Brain	0.018	0.068
Breasts	0.021	0.078
Gallbladder Wall	0.036	0.133
LLI Wall	0.094	0.347
Small Intestine	0.047	0.175
Stomach	0.029	0.107
ULI Wall	0.069	0.255
Heart Wall	0.075	0.278
Kidneys	0.129	0.477
Liver	0.152	0.563
Lungs	0.062	0.230
Ovaries	0.026	0.095
Muscle	0.013	0.047
Pancreas	0.030	0.110
Red Marrow	0.029	0.107
Bone Surfaces	0.030	0.111
Skin	0.019	0.069
Spleen	0.088	0.327
Thymus	0.023	0.086
Testes	0.019	0.072
Thyroid	0.020	0.074
Bladder Wall	0.019	0.070
Uterus	0.029	0.109
Total Body	0.024	0.090

Tumour Mass (g)	S factor rad/uCi-h	Dose Gy	Dose rad
0.1	2.25	17.80	1779.75
0.5	0.48	3.80	380.47
1.0	0.25	1.97	196.96
2.0	0.13	1.00	99.67

Table 8 Maximum Radiation Dose Estimate for ^{131}I-B72.3

Organ	Total Dose mGy/MBq	Total Dose rad/mCi
Adrenals	0.821	3.038
Brain	0.514	1.902
Breasts	0.603	2.231
Gallbladder Wall	0.913	3.378
LLI Wall	2.24	8.288
Small Intestine	1.3	4.810
Stomach	1.15	4.255
ULI Wall	1.69	6.253
Heart Wall	1.82	6.734
Kidneys	2.41	8.917
Liver	1.92	7.104
Lungs	1.55	5.735
Muscle	0.473	1.750
Ovaries	0.768	2.842
Pancreas	0.858	3.175
Red Marrow	0.783	2.897
Bone Surfaces	0.678	2.509
Skin	0.547	2.024
Spleen	2.04	7.548
Testes	0.595	2.202
Thymus	0.717	2.653
Thyroid	44.6	165.020
Bladder Wall	0.755	2.794
Uterus	1.13	4.181
Total Body	0.715	2.646
Effective Dose	3.45 mSv/MBq	12.765 rem/mCi

(Tumour not included)

Tumour Mass (g)	S factor	Dose per mCi Gy	rad
0.1	3.6	982	98275
0.5	0.759	207	20720
1	0.393	107	10728
2	0.2	54	5460

Contribution to organ dose from activity in tumour

It is assumed that the tumour is a small source located in the lower trunk which will make a contribution to all other organ doses. So that the computer software program known as MIRDOSE3 can be used, the activity is assumed to be located in the ovaries.

The ovary dose given in above was calculated separately. It is not the tumour dose.

Bladder Residence Time - The activity excreted via the bladder is almost insignificant. The total bladder and urine residence times in Table 5 was used as the urine activity in the dose calculation. No excretion model or assumed voiding time were used.

Table 9. Maximum Radiation Dose Estimates for ^{90}Y

Organ	Total Dose mGy/MBq	Total Dose rad/mCi
Adrenals	0.57	2.109
Brain	0.57	2.109
Breasts	0.57	2.109
Gallbladder Wall	0.57	2.109
LLI Wall	3.47	12.839
Small Intestine	1.36	5.032
Stomach	0.709	2.623
ULI Wall	2.25	8.325
Heart Wall	1.8	6.660
Kidneys	7.87	29.119
Liver	2.89	10.693
Lungs	1.88	6.956
Muscle	0.232	0.858
Ovaries	0.57	2.109
Pancreas	0.57	2.109
Red Marrow	0.964	3.567
Bone Surfaces	1.03	3.811
Skin	0.57	2.109
Spleen	2.32	8.584
Testes	0.57	2.109
Thymus	0.57	2.109
Thyroid	1.72	6.364
Bladder Wall	0.444	1.643
Uterus	0.57	2.109
Total Body	0.645	2.387

Tumour Mass (g)	S rad/uCi-h	Dose per mCi Gy	rad
0.1	8.97	546	54585
0.5	2.51	152.7	15274
1	1.4	85.2	8519
2	0.758	46.1	4613

Contribution to organ dose from activity in tumour

It is assumed that the tumour is a small source located in the lower trunk which will make a contribution to all other organ doses. So that the computer software program known as MIRDOSE3 can be used, the activity is assumed to be located in the ovaries. The ovary dose given in above was calculated separately. It is not the tumour dose.

Bladder Residence Time: The activity excreted via the bladder is almost insignificant. The total bladder and urine residence times in Table 5 was used as the urine activity in the dose calculation. No excretion model or assumed voiding time were used.

Table 10. Radiation Dose Estimate for ^{131}I-B72.3 (7 days)

Organ	Total Dose mGy/MBq	Total Dose rad/mCi
Adrenals	0.377	1.395
Brain	0.24	0.888
Breasts	0.276	1.021
Gallbladder Wall	0.418	1.547
LLI Wall	1.02	3.774
Small Intestine	0.587	2.172
Stomach	0.52	1.924
ULI Wall	0.769	2.845
Heart Wall	0.863	3.193
Kidneys	1.13	4.181
Liver	0.888	3.286
Lungs	0.727	2.690
Muscle	0.212	0.784
Ovaries	0.35	1.295
Pancreas	0.393	1.454
Red Marrow	0.358	1.325
Bone Surfaces	0.309	1.143
Skin	0.25	0.925
Spleen	0.951	3.519
Testes	0.272	1.006
Thymus	0.328	1.214
Thyroid	17.8	65.860
Bladder Wall	0.338	1.251
Uterus	0.497	1.839
Total Body	0.323	1.195

Tumour Mass (g)	Dose to 24 hour rad/mCi
0.1	2991
0.5	631
1	327
2	166

Table 11. Radiation Dose Estimates for ^{90}Y (7 days)

Organ	Total Dose mGy/MBq	Total Dose rad/mCi
Adrenals	0.5	1.850
Brain	0.365	1.351
Breasts	0.5	1.850
Gallbladder Wall	0.5	1.850
LLI Wall	2.87	10.619
Small Intestine	1.14	4.218
Stomach	0.603	2.231
ULI Wall	1.87	6.919
Heart Wall	1.53	5.661
Kidneys	6.5	24.050
Liver	2.41	8.917
Lungs	1.58	5.846
Muscle	0.194	0.718
Ovaries	0.4	1.480
Pancreas	0.5	1.850
Red Marrow	0.808	2.990
Bone Surfaces	0.858	3.175
Skin	0.5	1.850
Spleen	1.97	7.289
Testes	0.5	1.850
Thymus	0.5	1.850
Thyroid	1.43	5.291
Bladder Wall	0.38	1.406
Uterus	0.5	1.850
Total Body	0.546	2.020

Tumour Mass (g)	rad/mCi at 24 hour
0.1	6925
0.5	1938
1	1081
2	585

Radiotherapeutic Study

Radiotherapeutic Study was conducted in two parts.

Part A where the theoretical doses to target and non-target organs were calculated for the analogous radioimmunoconjugates.

Part B where the various radioactive levels of ^{64}Cu-SarAr-B72.3 was injected into tumour bearing mice and the therapeutic effect of the product was monitored as an extension of animal survival time.

Radiotherapeutic Study - Part A

Biodistribution studies of ^{123}I- and ^{111}In- radiolabelled B72.3 were conducted in LS174t tumour bearing nude mice (see Table 5,6) Standard calculations were performed using computer software MIRDOSE 3 which was used to compare target to non-target dose of their analogous therapeutic counterparts (^{90}Y and ^{131}I respectively) with ^{64}Cu-SarAr-B72.3 (see Table 7,8,9)

Theoretical maximum accumulated dose (which is equivalent to 10 half life decay) for each radioimmunoconjugate was calculated. Total body dose for ^{64}Cu-SarAr-B72.3 was significantly lower (0.09 rad/mCi) than analogous products (^{131}I-B72.3, 2.64 rad/mCi; ^{90}Y-B72.3, 2.387 rad/mCi). Comparative maximum doses to tumours of various sizes was calculated. Doses for ^{131}I- and ^{90}Y-B72.3 appear to be better than for ^{64}Cu-SarAr-B72.3. However, the lack of stability of the radioimmunoconjugate at the tumour site in real biological systems prevents the tumour from receiving the maximum accumulated dose.

Hence doses to target and non-target organs were re-calculated assuming the radioimmunoconjugates (^{131}I and ^{90}Y) were stable for approximately 24 hours at the tumour site and the non-target organs were dosed for up to 7 days allowing for natural biological clearance. MIRDOSE 3 was used to re-calculate dose to various organs under these conditions (see Table 10,11). Most relevant resultant target to non-target ratios are given in Table 12.

Table 12 Ratio of Target:Non-Target Doses for each Radioimmunoconjugate

	^{64}Cu	^{131}I	^{90}Y
Tumour (0.1g):Kidneys	2094	716	288
Tumour (0.1g):Liver	1795	906	776
Total Body Dose for 7 days	0.09	1.195	2.020

*MIRDOSE 3 was used to estimate human organ doses assuming the residence times in man are the same as the animal model. It is acknowledged that this affects the accuracy of the dose estimates.

Radiotherapeutic Study - Part B.

In order to assess therapeutic effect of ^{64}Cu, in a real biological system, nude mice bearing LS174t colorectal carcinoma were injected with various doses (0, 10, 20, 30, 40 MBq) of ^{64}Cu-SarAr-B72.3.

Results are given in Table 13 and a typical profile of a study is given in Figure 1. For all activity levels greater than 20 MBq a significant extension in mouse life was achieved. Experimental details follow.

Table 13 Extension of mouse life relative to ^{64}Cu-SarAr-B72.3 - Part B

Experiment	Survival[1] (Days)
Control[2]	20-25
10 MBq	30-35
20 MBq	60-70
30 MBq	40-45
40 MBq	30-35

[1]Greater than 30 % of animals; [2]Greater than 50 control animals;

Figure 1. Radiotherapeutic effect of 30 MBq of ^{64}Cu-SarAr-B72.3 in tumour bearing mice.

Experimental for Radiotherapeutic Study - Part B

Animal model: LS174t tumour tissue from nude mice was transplanted into nude mice for each experiment.

Animal selection: Only animals bearing tumours 3.5 - 5.5 mm 7 days post transplantation were selected for each study. Up to 10 animals per dose.

Injection: The product was injected into the nude mice on Day 7 after transplantation of tumour tissue.

Doses: Various activities of Cu-64-SarAr-B72.3 was injected into the mice. Control animals receive only antibody.

Monitoring of animals: Animals were monitored for changes in tumour size
Animal mass
Behavioural and physical abnormalities
(e.g. movement / gait , food intake and hunching)
(For any of the above characteristic, frequency of weighing increased)

Histology, Haematology and Biochemistry:

Animals were sacrificed at pre-determined time points (2 days, 1, 2, 3, 4 weeks, 2, 3, 4, 5 and 6 months).
Radiotoxic effects were monitored.
(conducted by external pathologist of Department of Veterinary Anatomy and Pathology, University of Sydney)

Endpoint of the study:

1) Body weight loss > 20 %.

2) Rapid weight loss of > 10% overnight.

3) Ulceration of tumour

4) Limitation of normal behaviour (e.g. ability to feed or drink).

5) Tumour size 10 x 10 mm (UK Cancer Council)

Example 7

In accordance with the description of the invention provided above specific preferred pharmaceutical compositions of the present invention may be prepared, and examples of which are provided below. The following specific formulations are to be construed as merely illustrative examples of formulations and not as a limitation of the scope of the present invention in any way.

A compound of Formula (I) may be administered alone, although it is preferable that it be administered as a pharmaceutical formulation.

Example 7(a) - Composition for Parenteral Administration

A pharmaceutical composition of the present invention for intramuscular injection could be prepared to contain 1 mL sterile isotonic saline, and 1 mg of compound of Formula (I).

Similarly, a pharmaceutical composition for intravenous infusion may comprise 250 ml of sterile Ringer's solution, and 5 mg of compound of Formula (I).

Example 7(b) - Injectable Parenteral Composition

A pharmaceutical composition of this invention in a form suitable for administration by injection may be prepared by mixing 1% by weight of compound of Formula (I) in 12% by volume propylene glycol and isotonic saline. The solution is sterilised by filtration.

Modifications and variations such as would be apparent to a skilled addressee are deemed to be within the scope of the present invention. It is to be understood that the present invention should not be limited to the particular embodiment(s) described above. Throughout the specification, unless the context clearly indicates otherwise, the word, "comprise", "comprises", "comprising" or other variations thereof shall be understood as meaning that the stated integer is included and does not exclude other integers from being present even though those other integers are not explicitly stated.

Further, the present invention relates to all steps, compounds, intermediates as well as final products.

a dione of formula

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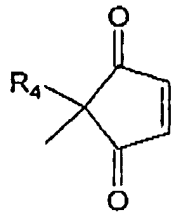
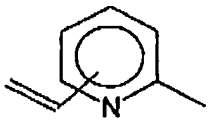
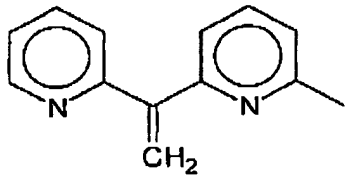


a substituted vinyl group of formula Het^1-C(Het^2)=CH_2 where Het^1 and Het^2 are the same or different and is each a nitrogen containing heterocyclic group or Het^1 is a nitrogen containing heterocyclic group and Het^2 is H, -C(=NH)OR^2, NCO, NCS, COR", COOR', SR^2, $NHNR^2R^3$, $NHCONHNR^2R^3$, $NHCSNHNR^2R^3$, $CONR^2$, OR^2, NR^2R^3, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$, and $(CHCH)_rArR^1$ where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, -$(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$ and $(CHCH)_rArR^1$ and where R^1 is selected from SH, OH, NH_2, COOH, NCS, -N=N, or -C(=NH)OCH_3 and, COR", where R" is H, halogen, N_3, alkoxy, OAr, imidyloxy, imidazoyloxy, alkyl, or alkyl substituted with a halogen or other leaving group, where p is an integer from 1 to 20, q is an integer from 1 to 20, r is an integer from 1 to 4, and Ar is optionally substituted aryl or optionally substituted aralkyl, provided that when one of X and Y is selected from C-NO_2, C-OH, C-Cl, C-CH_3 or C-NH_2 then the other X or Y substituent cannot be selected from C-NO_2, C-OH, C-Cl or C-NH_2.

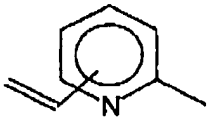
4. A compound according to claim 3, wherein the functionalised linkage group Z of the compound of Formula (I) is a vinyl pyridyl group of formula

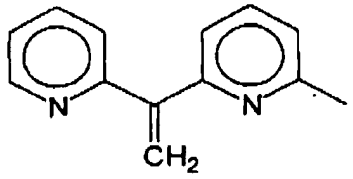


or



5. A compound according to claim 1, wherein the functionalised linkage group Z of the compound of Formula (I) is selected from





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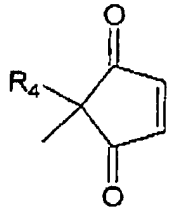


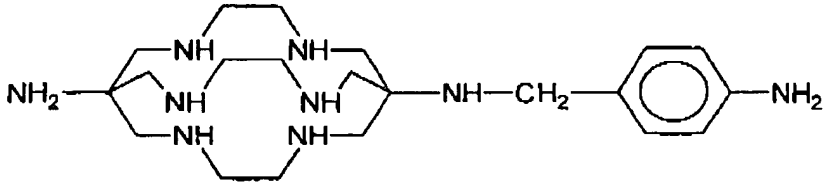
, and

NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $-(CH_2OCH_2O)_qArR^1$, $-(CHCH)_rR^1$, and $(CHCH)_rArR^1$ and where R^1 is selected from NH_2, COOH, NCS, NCO, -N=N, $-C(=NH)OCH_3$, and COR" where R" is H, halogen, alkyl, or alkyl substituted with a halogen or other leaving group, where p is an integer from 1 to 20; q is an integer from 1 to 20; r is an integer from 1 to 4; and Ar is optionally substituted aryl or optionally substituted aralkyl, provided that at least one of R^2 and R^3 is other than hydrogen.

6. A compound according to claim 1, wherein W is NH and Z is selected from NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, and $(CH_2)_pArR^1$; R^1 is selected from NH_2, COOH and NCS; and p is an integer from 1 to 4.

7. A compound according to claim 5, wherein the Z group of said compound of Formula (I) is NR^2R^3 where R^2 and R^3 together with the nitrogen atom to which they are attached form an optionally substituted saturated or partially unsaturated ring optionally containing one or more further heteroatoms O, S or N whereby there is at least one substituent capable of binding said compound of Formula (I) with a molecular recognition unit.

8. A compound of Formula (I) having the following structure:



9. A compound according to claim 1, wherein said compound is complexed with a metal ion.

10. A compound according to claim 9 wherein the metal ion is selected from Cu, Tc, Gd, Ga, In, Y, Co, Re, Fe, Au, Ag, Rh, Pt, Bi, Cr, W, Ni, V, Pb, Ir, Pt, Zn, Cd, Mn, Ru, Pd, Hg, Ti, and the lanthanide group of elements in the Periodic Table such as Sm, Ho, Gd, Tb, Sc.

11. A compound according to claim 10 wherein the metal ion is a radionuclide selected from the group of Cu, Cu, Tc, In, Gd, Ga, Fe, Cu, Ti and other radionuclides from the Lanthanides, Re, Sm, Ho, and Y .

12. A compound according to claim 11 wherein the radionuclide is selected from the group of ^{64}Cu, ^{67}Cu and ^{99m}Tc.

13. A pharmaceutical formulation comprising a compound according to claim 1, a radiolabelled complex or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

14. A diagnostic formulation comprising a compound according to claim 1, a radiolabelled complex or pharmaceutically acceptable salt thereof and a reducing agent in a pharmaceutically acceptable carrier.

15. A method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof.

16. Use of a compound according to claim 1 or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof in the preparation of a medicament for diagnosis or therapy of disease in a subject.

17. A compound according to claim 1 or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof when used in the diagnosis or therapy of disease in a subject.

18. A conjugate compound comprising at least one compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof bonded to at least one molecular recognition unit comprising an antibody, protein, peptide, carbohydrate, oligonucleotide, oligosaccharide.

19. A method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a conjugate compound according to claim 18.

20. Use of a conjugate compound according to claim 18 in the preparation of a medicament for diagnosis or therapy of disease in a subject.

21. A conjugate compound as described in claim 1 when used in the diagnosis or therapy of disease in a subject.

22. A method of imaging a subject comprising introducing a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof to a subject.

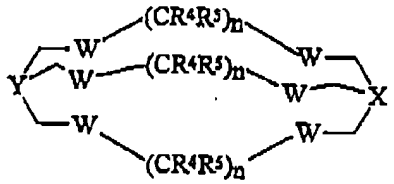
23. Use of a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof in the preparation of a medicament for imaging in a subject.

24. A compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof when used in imaging in a subject.

AMENDED CLAIMS

[received by the International Bureau on 08 May 2000 (08.05.00): original claims 1-24 replaced by new claims 1-23 (5 pages)]

1. A compound which is capable of being radiolabelled of general formula (I) which is as follows:



(I)

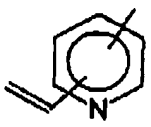
in which n represents an integer from 2 to 4,

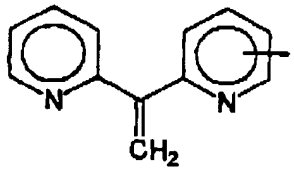
where each R^4 and R^5 is independently selected from -H, CH_3, COOH, NO_2, CH_2OH, H_2PO_4, HSO_3, CN, $C(=O)NH_2$ and CHO;

X and Y are the same or different and are selected from the group consisting of C-R, N, P and C-Z in which R is selected from hydrogen, halogen, hydroxyl, nitro, nitroso, amino, optionally substituted alkyl, optionally substituted aryl, optionally substituted aralkyl, cyano, COOR', COCOOR', $NH\text{-}COCH_2Br$ and -NH-CO-CH=CH-COOR' in which R' is a hydrogen atom or alkyl group;

W is selected from the group consisting of NH, S and O; and

Z is a functionalised linkage group which is capable of binding said compound of formula (I) to a molecular recognition unit, selected from the group consisting of $C(=NH)OR^2$, NCO, NCS, SR^2, $NHNR^2R^3$, $NHCONHNR^2R^3$, $NHCSNHNR^2R^3$, $CONR^2R^3$, NR^2R^3, $(CH_2)_pR^6$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$, $(CHCH)_rArR^1$, maleimide, a vinyl pyridyl group of formula





or

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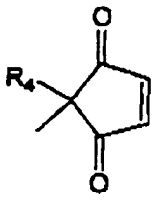


and a substituted vinyl group of formula Het^1-C(Het^2)=CH_2, where Het^1 and Het^2 are the same or different and each is a nitrogen containing heterocyclic group or Het^1 is a nitrogen containing heterocyclic group and Het^2 is H; where

R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $-(CH_2OCH_2O)_qArR^1$, $(CHCH)_rR^1$ and $(CHCH)_rArR^1$, with the proviso that when R^2 is H, R^3 is not H;

R^1 is selected from SH, OH, NH_2, COOH, NCS, -N=N, or -C(=NH)OCH_3 and, COR", where R" is H, halogen, N_3, alkoxy, OAr, imidyloxy, imidazoyloxy, alkyl, or alkyl substituted with a halogen or other leaving group; and

R^6 is selected from SH, NH_2, COOH, NCS, -N=N, or -C(=NH)OCH_3 and, COR";

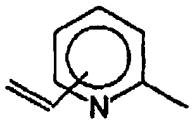
and

p is an integer from 1 to 20, q is an integer from 1 to 20, r is an integer from 1 to 4, and Ar is optionally substituted aryl or optionally substituted aralkyl; and wherein

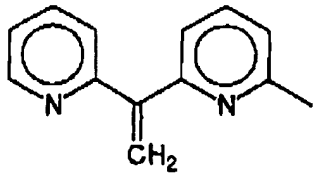
at least one of X and Y is C-Z, or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein the molecular recognition unit is selected from the group consisting of an antibody, protein, peptide, carbohydrate, nucleic acid, oligonucleotide, oligosaccharide and liposome.

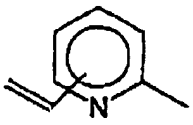
3. A compound according to claim 1, wherein the functionalised linkage group Z of the compound of Formula (I) is a vinyl pyridyl group of formula

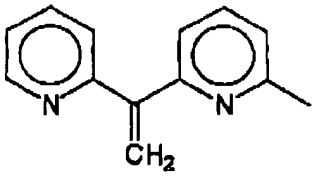


or



4. A compound according to claim 1, wherein the functionalised linkage group Z of the compound of Formula (I) is selected from





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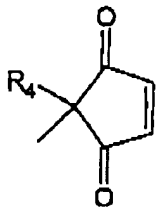


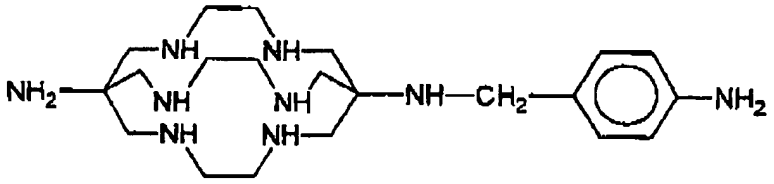
, and

NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, $(CH_2)_pArR^1$, $(CH_2O)_pCH_2R^1$, $-(CH_2OCH_2O)_qArR^1$, $-(CHCH)_rR^1$, and $(CHCH)_rArR^1$, with the proviso that when R^2 is H, R^3 is not H, and where R^1 is selected from NH_2, COOH, NCS, NCO, -N=N, $-C(=NH)OCH_3$, and COR'' where R'' is H, halogen, alkyl, or alkyl substituted with a halogen or other leaving group, where p is an integer from 1 to 20; q is an integer from 1 to 20; r is an integer from 1 to 4; and Ar is optionally substituted aryl or optionally substituted aralkyl, provided that at least one of R^2 and R^3 is other than hydrogen.

5. A compound according to claim 1, wherein W is NH and Z is selected from NR^2R^3 where R^2 and R^3 are the same or different and are independently selected from H, $(CH_2)_pR^1$, and $(CH_2)_pArR^1$, with the proviso that when R^2 is H, R^3 is not H; R^1 is selected from NH_2, COOH and NCS; and p is an integer from 1 to 4.

6. A compound according to claim 4, wherein the Z group of said compound of Formula (I) is NR^2R^3 where R^2 and R^3 together with the nitrogen atom to which they are attached form an optionally substituted saturated or partially unsaturated ring optionally containing one or more further heteroatoms O, S or N whereby there is at least one substituent capable of binding said compound of Formula (I) with a molecular recognition unit.

7. A compound of Formula (I) having the following structure:



8. A compound according to claim 1, wherein said compound is complexed with a metal ion.

9. A compound according to claim 8 wherein the metal ion is selected from Cu, Tc, Gd, Ga, In, Y, Co, Re, Fe, Au, Ag, Rh, Pt, Bi, Cr, W, Ni, V, Pb, Ir, Pt, Zn, Cd, Mn, Ru, Pd, Hg, Ti, and the lanthanide group of elements in the Periodic Table such as Sm, Ho, Gd, Tb, Sc.

10. A compound according to claim 9 wherein the metal ion is a radionuclide selected from the group of Cu, Cu, Tc, In, Gd, Ga, Fe, Cu, Ti and other radionuclides from the Lanthanides, Re, Sm, Ho, and Y .

11. A compound according to claim 10 wherein the radionuclide is selected from ^{64}Cu and ^{67}Cu.

12. A pharmaceutical formulation comprising a compound according to claim 1, a radiolabelled complex or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier.

13. A diagnostic formulation comprising a compound according to claim 1, a radiolabelled complex or pharmaceutically acceptable salt thereof and a reducing agent in a pharmaceutically acceptable carrier.

14. A method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof.

15. Use of a compound according to claim 1 or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof in the preparation of a medicament for diagnosis or therapy of disease in a subject.

16. A compound according to claim 1 or a metal complex, radiolabelled complex or pharmaceutically acceptable salt thereof when used in the diagnosis or therapy of disease in a subject.

17. A conjugate compound comprising at least one compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex or a pharmaceutically acceptable salt thereof bonded to at least one molecular recognition unit comprising an antibody, protein, peptide, carbohydrate, oligonucleotide, oligosaccharide.

18. A method of diagnosis or therapy in a subject comprising administering to the subject a diagnostically or therapeutically effective amount of a conjugate compound according to claim 17.

19. Use of a conjugate compound according to claim 17 in the preparation of a medicament for diagnosis or therapy of disease in a subject.

20. A conjugate compound as described in claim 1 when used in the diagnosis or therapy of disease in a subject.

21. A method of imaging a subject comprising introducing a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof to a subject.

22. Use of a compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof in the preparation of a medicament for imaging in a subject.

23. A compound of Formula (I) according to claim 1 or a metal complex, radiolabelled complex, conjugate compound or pharmaceutically acceptable salt thereof when used in imaging in a subject.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

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in its capacity as elected Office

Date of mailing (day/month/year) 15 September 2000 (15.09.00)	
International application No. PCT/AU00/00003	**Applicant's or agent's file reference** 440423C
International filing date (day/month/year) 05 January 2000 (05.01.00)	**Priority date** (day/month/year) 05 January 1999 (05.01.99)
Applicant SMITH, Suzanne, Virginia et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

04 August 2000 (04.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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